Medical Lib.
AUG 15 1921

Volume V July, 1921 *Number 4*

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

Single Copies, $1.25
$6.00 Per Year

Published bi-monthly by
The Association *for the* Study *of* Internal Secretions
1100-1103 Title Insurance Building
Los Angeles, California

ACCEPTED

FOR INCLUSION IN

"New and Non-official Remedies"

The New Germicide
MERCUROCHROME

(Readily soluble in water in required percentages)

Mercurochrome has proved effective as a germicide in the treatment of various infections of the GENITO-URINARY TRACT and in OPHTHALMOLOGY. It has also been successfully used in OTITIS MEDIA, in the treatment of DIPHTHERIA CARRIERS and to some extent as a local germicide in SURGERY.

Literature Upon Request

Hynson, Westcott & Dunning

BALTIMORE

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*
Internal Secretions

July, 1921

THE PARATHYROID GLANDS

A REVIEW OF THE LITERATURE

WALTER M. BOOTHBY, A.M., M.D.

Section of Clinical Metabolism
Mayo Clinic and The Mayo Foundation
Graduate School, University of Minnesota

ROCHESTER, MINNESOTA

I. ANATOMY AND PHYSIOLOGY

Sandström (1880) was the first to describe the (external) parathyroid glands as anatomic entities; his gross and microscopic description of these bodies as found in man and in several types of animals is excellent. He thought that they probably represented undeveloped embryonic thyroid tissue. Sandström credited both Remak (1851) and Virchow (1864) with having seen these bodies and briefly described them. Baber, in a second paper on the thyroid published in 1881, apparently without knowledge of Sandström's work, devoted a special section to describing under the name of "undeveloped portions of the thyroid" what we now recognize as the external and internal parathyroids. He found no evidence, however, of their later development into thyroid tissue. Unfortunately Baber's work remained comparatively unknown and the confusion resulting from the failure to recognize an irregular and quite extensive distribution of parathyroid tissue was not completely cleared up until the work of Kohn was published in 1895. Biedl (1913)

credits Stieda (1881) with having described under the name of carotid glands the parathyroids in sheep embryos. Horsley (1886) as a result of an extensive experimental study came to the conclusion that the "undeveloped tissue" of Baber was not embryonic thyroid tissue because after partial thyroidectomy there was hypertrophy of the remaining thyroid lobe with an increase both in the number and in the size of the cells so that there was a plication of the acinal wall, but without metamorphosis of the "embryonic" tissue into thyroid acini.

Gley (1891) reviewed about 300 reported experimental thyroidectomies and found that death occurred almost always from tetany soon after the operation. He suggested that certain "glandes thyroides surnumeriaires" (external parathyroids), which he had observed first in rabbits, played a rôle in the syndrome.

The fact that tetany might follow thyroidectomy was first recognized in Billroth's clinic by Weiss in 1881. Schiff (1884) demonstrated that after complete removal of the thyroid gland certain animals, notably cats and dogs, usually developed spastic or fibrillary contractions, tetany, followed by death. This was confirmed by Wagner (1884), Carle (1888), von Eiselsberg (1889) and others. At the time Gley presented his first paper he apparently did not know of either Sandström's or Baber's work, although later he referred frequently to Sandström's excellent paper. In a most interesting series of communications before the Societé de Biologie (Paris) beginning in 1891, Gley presented his evidence that thyroidectomy does not produce fatal tetany unless the "glandules thyroidiennes" (external parathyroids), the term he preferred to Sandström's "parathyroid," likewise are removed. Because he found that removal of the "glandules thyroidiennes" without the thyroid did not cause fatal tetany in the animal on which he experimented and because he found that these glands usually develop to twice their original size after thyroidectomy, he considered, as had Sandström, the "glandules thyroidiennes" to be embryonic thyroid tissue which possessed the power of taking on the thyroid function, at least in part. Gley may, therefore, be credited with having rediscovered the external parathyroid glands and of being the first to show that they are of physiologic importance.

Cristiani (1892), by the method of serial sections, showed that in the rat the parathyroids are embedded in the thyroid and that it would be impossible in this animal to spare them when doing a thyroidectomy. In the mouse he found (1893) a similar but less perfect incorporation, while in the fieldmouse one parathyroid was usually inside and the other outside the thyroid, although there was considerable individual variation in their location. Nicolas (1893) found four parathyroids in bats. Chantemesse and Marie (1893) showed that in man the external parathyroids could readily be spared in thyroidectomy and in 1907 Getzowa described in man cells situated in the thyroid that resembled parathyroid tissue.

The experimental work of Gley was confirmed by Verstraeten and Vanderlinden (1894) and they likewise considered the external parathyroids part of the thyroid gland. Moussu (1892), however, very emphatically opposed Gley's conception of the importance of the parathyroids and showed that some animals survived even "complete" thyroidectomy and that age played an important rôle in the determination of the reaction. Hofmeister (1892) stated that those animals that survived developed nutritive disturbances of one of two types which he designated as "cretinism myxoedemateux" or "cretinism atrophique." Moussu (1893) found that although the parathyroids enlarge after thyroidectomy they do not show the slightest tendency to develop the structure of the thyroid, also shown by Horsley, nor do they prevent the postoperative myxedema noted by Hofmeister. He therefore strongly maintained that they do not take over the function of the thyroid and he doubted very much if they had any real important function; if they did he suggested that it was distinct from the function of the thyroid.

Kohn, in 1895, in a very excellent article, described in detail the two "external epithelial bodies," a name which he preferred to the term "parathyroid" of Sandström or "Glandule thyroidienne" of Gley. His main contribution, however, was emphasizing the importance (in the cat) of similar tissue situated within the thyroid gland and designated by him as the "internal epithelial bodies"; these areas had been seen by several previous observers who, however, had laid no particular stress on their importance in explaining the different reactions produced by

thyroidectomy in different species (Baber 1881, Maurer 1887, Rogowitch 1888, Cristiani 1893). Hürthle (1894) also had seen this internal parathyroid tissue, but considered it the same as the masses of interacinous cells described by Wölfler (1880) and which were supposed by the latter to develop into alveolar cells and acini and which have often been considered the nuclei of thyroid adenomas. Zerlinska (1894), on the other hand, described embryologic "Läppchen" in the thyroid which he said must not be confused with the "Zellhaufen" of Wölfler; he considered them identical with the bodies described by Gley and Cristiani. Groschuff (1896), as a result of extensive embryologic studies, believed the parathyroids to be organs separate and distinct from the thyroid. Verdun (1898) showed that the parathyroids are entodermal glands and come from the dorsal part of the third and fourth branchial pouch.

Blumreich and Jacoby (1896), working on cats, carried out quite an extensive series of thyroparathyroidectomies and partial thyroidectomies with irregular results; in many instances they did not obtain tetany as a result of what they considered a complete extirpation of all thyroid and parathyroid tissue.

Vassale and Generali, in a series of papers between 1896 and 1900, completely demonstrated, however, that the removal of all parathyroid tissue, even with the preservation of thyroid tissue, led to fatal tetany while no tetany resulted from removal of the thyroid if one of the four parathyroids remained intact and capable of functioning. Because of the constancy of parathyroids in all mammals, because they have a characteristic and stable structure even in thyroidectomized animals, and like other glands grow by karyokinesis, because if spared at thyroidectomy they do not prevent the development of cretinism and myxedema, and because their complete removal results in fatal tetany, Vassale and Generali (1896) did not accept Gley's contention that they are embryologic thyroid rests but believed that they are special organs of metabolism with a metabolic function yet to be determined but distinct from that of the thyroid. Moussu (1893) had previously but almost parenthetically suggested that the parathyroids might have a separate function; his main contention, however, had been that they are unimportant

bodies, and not until the publication of Vassale and Generali's article proving that the glands have a distinct and important function did Moussu (1897) strenuously maintain the latter view. Gley (1897) did not entirely accept the conceptions of Moussu and of Vassale and Generali, but admitted that the parathyroids might assume the function of the thyroid or complete the function of the thyroid, or finally, that they might have a separate function. As late as 1901 Gley believed that a true functional association might possibly exist between the thyroid and the parathyroids and that they played a more causative rôle in exophthalmic goiter than does the thyroid.

Jeandelize (1903) from an extensive study came to the conclusion that the parathyroids are independent organs. Erdheim (1906) reached the same conclusion as the result of a most careful series of experiments in which he found that in the animals which developed tetany no parathyroid tissue remained, its absence being proved by serial cross-sections; he also found that the individual differences in reaction after parathyroidectomy were marked and that the symptoms of tetany usually reached their height in the first twenty-four hours and then in some cases became chronic and were accompanied by nutritive changes, evidenced by an excessive growth of the lower incisors; this latter observation was apparently confirmed by Hohlbaum (1912). Erdheim also studied by serial sections three patients who died of postoperative tetany; in none of these could he find any trace of parathyroid tissue. He also established some evidence that the tetany of pregnancy likewise is due to parathyroid insufficiency.

With the exception of Vincent and Jolly (1905) and Forsyth (1908) no one has recently questioned the importance of the parathyroids or the fact that their complete extirpation usually results in tetany followed by death. Vincent, in 1920, retracted the conclusions based on his earlier work with Jolly so that we may now consider the theory completely accepted that the thyroid and parathyroids are independent organs and that the removal of the parathyroids quickly results in death from tetany in the majority of instances and in most species. In herbivora tetany does not always occur; MacCallum, Thomson and Murphy (1907) had a large preponderance of negative

results in goats and sheep; they cannot explain these results except on the ground that some parathyroid tissue may have been overlooked, although none was found in a most careful search. Iselin (1908) obtained violent tetany from parathyroidectomy (with preservation of the thyroid) in young rats, although in older rats often it did not occur and then only after a longer interval and in milder form. Simpson (1911 and 1913) also found variability in reaction apparently dependent on age. Thompson and Leighton (1908) found, following the gradual destruction of the parathyroids in the dog, a train of symptoms different from those caused by excision of the glands. After ligation of all parathyroid tissue the dog passes practically without symptoms the time limits of tetanic death that occurs after excision of the glandules; gradually, however, chronic symptoms trophic in nature arise, consisting of progressive loss of weight and strength, greatly diminished resistance to infection, and a final stuperous condition ending in death without tetany.

MacCallum (1911 and 1912) and MacCallum and Vogel (1913) by cross-circulation experiments have shown that the hyperexcitability of the nervous system is peripheral and that it is dependent on some change in the character of the blood; they believe that the blood of an animal in tetany contains something that renders the peripheral nerve ganglion and the nerve endings hypersensitive and that the spasm of the muscles comes only when the ganglion cells send out abnormally violent impulses to abnormally sensitive nerve-endings. MacCallum and Vogel (1913) showed that if the blood from an animal with tetany is perfused in a normal leg the excitability to the nerves rises to a characteristically high level and that the addition of parathyroid extract to the blood has little or no effect in lowering this excitability. Parathyroid extract when injected into the circulation of an animal in tetany, fails to reduce markedly or permanently the excitability of the nerves, although it seems to affect the more sensitive ganglion cells, thus cutting off excessive impulses to the periphery; although the nerves remain hyperexcitable, tetany is usually much diminished or entirely abolished, an action analogous to that of ether. Direct analysis of the blood shows that the blood of an animal in tetany, compared with the normal blood, is very poor in calcium; adminis-

tration of parathyroid does not increase the calcium content. However, blood transfusion was found by Jacobson (1912) to have no immediate or marked action on the course of the tetany. Mustard (1911) showed that parathyroid tetany is not affected by the removal of the cerebral mortor cortex or by rendering the limb aspastic through section of its afferent nerves and concluded that apparently the tetany depends not only on a local increase of motor excitability in the spinal cord, but also on the nervous connections with some region of the encephalon below the cerebral cortex. Carlson and Jacobson (1911) found that transsection of the cord stops parathyroid tetany, but not the tetany produced by ammonia poisoning when the latter is severe. Carlson (1912 and 1913) showed that in parathyroid tetany in cats and dogs there are no spasms, contractures, or other evidences of hyperexcitability or tetany of the neuromuscular mechanisms of the digestive tract; even in very severe tetany the movements of the stomach and intestine may be normal; the variation from normal is depression or paralysis; the gastric and pancreatic digestion appear normal but retarded and there is an absence of hunger. Keeton (1914) showed a depression of both total and free acid.

Halstead, in 1912, reported an experiment on a dog which lived fifteen months after complete thyroparathyroidectomy and transplantation of two of the parathyroids with a slice of the thyroid into the rectus muscle; the transplant was removed after a year and found to be mostly thyroid tissue with a trace of parathyroid tissue; the dog survived three months longer, finally dying of thyroparathyroid deficiency.

Morel and Rathery (1912) found in the liver following parathyroidectomy what they considered definite lesions that paralleled the intensity of the postoperative symptoms. Stoland (1914) obtained somewhat similar results. Boldyreff (1913) found that the body temperature of warm blooded animals is lowered by complete thyroparathyroidectomy and that by artificial heat it is possible to bring out typical tetanic attacks which in turn are relieved by cooling the animals.

Vassale, as early as 1898, showed that tetany after parathyroidectomy is intensified during pregnancy; this work was later confirmed from his laboratory by Massaglia (1913). In

1904 Vassale reported his results on the feeding of parathyroid extract in eclampsia. Werelius (1913) likewise showed that thyroparathyroidectomized dogs seemingly go into convulsions earlier in the later stages of pregnancy and die sooner than non-pregnant dogs and concluded therefore that probably fetal parathyroids do not compensate for the absence of the mother's glands. Carlson (1912) found in the dog but not in the cat that late pregnancy accelerates and intensifies parathyroid tetany in the majority of cases.

The experiments of Hoskins and Wheelon (1914) indicate that parathyroid destruction results in an increase of the vasomotor irritability, evidenced by reaction to nicotin, epinephrin, and pituitrin, but that there is no strict parallelism between the external symptoms of parathyroid deficiency and the degree of vasomotor irritability.

Simpson and Rasmussen (1914) at first believed that when animals are in pronounced parathyroid tetany, the coagulation time of the blood is prolonged; in their later work (1916), however, they could find no consistent effect.

From the experiments of Jackson (1916) it appears that the parathyroids continue to grow in young rats even when they are held at maintenance by underfeeding. Excessive meat diet, however, was shown by Tanberg (1916) not to cause hypertrophy of the parathyroids; he found no parathyroid hypertrophy following thyroidectomy nor any change in the structure of the former. Kojima (1917) could find no alteration in the pancreas as a result of parathyroidectomy, thus controverting the observations of Stoland (1914); Kojima likewise could produce no alterations in the islands of Langerhans by parathyroid feeding and he found no demonstrable change in the remaining parathyroid tissue as a result of partial parathyroidectomy.

Paton, Findlay and Watson (1917), as a result of their studies, conclude that the nervous symptoms following parathyroidectomy are due to the condition of the central nervous system; that the cerebral hemispheres are not directly involved in the production of spasticity, tremors, and jerkings, and that they may develop independently of the cerebellum, but its integrity is essential for a sustained spastic tone; that the integrity of the spinal cord is not essential since tetany persists after

section of the spinal neurones; that efferent neurones are the structures primarily implicated and that in advanced cases disturbed equilibrium suggests the involvement of the cerebellum. They do not believe that the increased electrical excitability can be taken as a measure of the severity of the condition and deny that the parathyroids exercise a direct controlling influence on the central nervous system. The relationship which Paton and Findlay point out between the symptoms of parathyroid tetany and guanidin poisoning will be considered later.

Honeyman (1919) controverted Uhlenhuth's (1918) hypothesis, that the thymus produces substances of a toxic nature in the blood which are normally antagonized by the parathyroids, by showing that extirpation of the thymus and of the parathyroids in the guinea pig does not modify in any way the onset of symptoms of *tetania parathyreopriva* and that it appears unlikely that the thymus secretes or contains any substance capable of producing tetany.

Houssay (1919) could find no constant reaction of voluntary muscle tissue produced by the action of blood serum from dogs in tetany different from that of normal dogs, thus confirming the observations of Wishart (1916).

In 1906 MacCallum presented an excellent anatomic description of the four parathyroid glands in man. He showed that they are located in the fatty areolar tissue, distinct from the intrinsic capsule of the thyroid. Aside from this, however, they have no very constant position and may be either high or low, internal or external, separated or more or less grouped, but usually they have a fairly close relationship to the four principal thyroid arteries; in consequence their blood supply may be decreased or cut off by ligation of these vessels. Halsted and Evans (1907) made very careful studies of the blood supply by the injection method and showed that the parathyroid glands in man are always supplied by definite parathyroid arteries which enter them at the hilus. The parathyroid arteries, superior and inferior, usually arise from the inferior thyroid, but frequently from anastomosing channels between the superior and inferior thyroid vessels. The excellent drawings represent not only the common types of vessels, but also the more infrequent types. They found little, if indeed any, direct vascular connec-

tion between the parathyroid gland and the connective tissue enveloping the thyroid. Iversen (1912) found two parathyroid glands on either side in 81 per cent of subjects studied; in 9 per cent there were three parathyroids, and in a few cases five. On an average they measure 6 by 4 by 2 mm. and are situated on the posterior border of the thyroid body at its inferior pole, in connection with the branches of the inferior thyroid artery and the recurrent laryngeal nerve.

Rhinehart (1912) has shown that both the thyroid and parathyroid glands are supplied entirely by nonmedulated nerves, apparently of the same origin.

MacCallum (1905), Erdheim (1906) and Kocher (1906) reviewed the occurrence of tetany in man after parathyroidectomy; the latter had nine patients who developed tetany out of forty who had total thyroidectomies; similar studies were made by Mayo and McGrath (1911), and by Pool (1915). von Eiselsberg (1915) reported fourteen mild cases of tetany, three severe cases, and three deaths from tetany in a series of 1300 operations for goiter. These authors recognized that tetany and *cachexia thyreopriva* are distinct and separate conditions. Halsted (1907) reviewed the subject of *parathyreopriva* together with the results of parathyroid transplantation; the reports on the results obtained proved disappointing.

II. PATHOLOGY

Vassale and Donazzio (1897) showed that degeneration occurs in certain tracts of the spinal cord following parathyroidectomy, but less frequently after thyroparathyroidectomy.

MacCallum and Fabyan (1907) reported a case of quite typical myxedema in which the thyroid was absent on postmortem examination but two apparently normal parathyroids were present and the hypophysis was hypertrophic. In consequence, they believed this case offered irrefragable proof of the complete independence of the thyroid and the parathyroid glands. Yanase (1907) found hemorrhage in the parathyroid glands in a high percentage of children who died from tetany, thus leading Escherich (1909) and others to lay great stress on the parathyroid origin of infantile tetany. Thompson and Harris (1908) in the study of the parathyroids in 250 routine

necropsies, found no definite lesions in the parathyroid. Bliss (1911) studied the parathyroids in twenty-two necropsies and found three instances of hemorrhage in the glands, one in a patient with bronchopneumonia; one in a patient with bronchopneumonia and pertussis, and one in a patient with bronchopneumonia with rachitis and syphilis. In two patients who died of infantile tetany he found no hemorrhage into the glands, although in one there was an increase in vascular and in connective tissue and he concluded therefore that there is no close connection between hemorrhagic lesions of the parathyroid glands and infantile tetany. Proescher and Diller (1912) report a case of tetany in which the necropsy showed hemorrhage into the parathyroids; in addition, however, there were an external fibrous pachymeningitis, chronic leptomeningitis, edema and hyperemia of the brain and spinal cord, as well as other pathologic lesions of the plexus, spleen, intestines, kidney and liver. As yet the evidence of a pathologic condition of the parathyroids in infantile tetany and in other types of tetany, except that following thyroidectomy, is meager and questionable and does not appear to justify the positive statements concerning the cause of infantile tetany which are frequently found in periodic literature.

Marine (1913), from his experiments on fowls, believed that their parathyroids are more susceptible to overgrowth than those of mammals. McCarrison (1914) states that of the offspring of goitrous parents a small percentage are born cretins, 63 per cent with congenital goiter, 32 per cent with congenital parathyroid disease, and 33 per cent with normal thyroid and parathyroid glands. In 1915 Harbitz reviewed the literature on parathyroid tumors and reported two new cases, the one an adenoma of the parathyroid with osteomalacia, and the other an adenoma of the parathyroid with *paralysis agitans*. The following year Wood reported several cases of parathyroid tumors of the tongue, and Schlagenhaufer two cases of tumor of the parathyroids.

Jackson (1916) found in experiments on young rats held at maintenance by underfeeding that, although growth of the parathyroids persisted, there was more or less nuclear and cytoplasmic degeneration. In confirmation of previous experiments,

Tanberg (1916) found that no structural change occurs in the parathyroids as a result of thyroidectomy. Allen (1920) noted marked hypertrophy of the parathyroids but no histologic changes following removal of the thyroid in the *Bufo larvae.*

III. CHEMISTRY

Gley (1891) and Laulanié (1891-1894) showed that the urine of completely thyroidectomized dogs is more toxic than that of normal dogs. Marfori (1893) found that intravenous injections of carbonate, lactate and tartrate of ammonia in dogs causes muscle twitchings and even tetany and opisthotonus together with irregular respiration and vomiting.

Sabbatani (1901) stimulated an interest in the relation of calcium to tetany by his observations that a solution of calcium applied to the brain diminishes its irritability to electric stimulation, but that substances that cause a precipitation of calcium such as oxalates or citrates cause an increased irritability. Stoeltzner (1906) advanced the hypothesis that tetany is due to an accumulation of calcium in the blood; his theories, however, have received no further confirmation except from the work of von Cybulski (1906) and of Schabad (1910), both of whom found slight calcium retention during active tetany and a greater retention during convalescence. Quest (1905), Cohn (1907), and Aschenheim (1910) analyzed the brains of children who died of tetany, and although there was a considerable diminution of the calcium content in some there was little regularity in the results.

Estes and Cecil (1907) reviewed the question of the iodin content of the parathyroids; they state that Gley (1897) showed the presence of iodin in the parathyroids and they point out that Mendel (1900) is widely misquoted as having found large quantities of iodin in these glands. Their own experiments confirmed the findings of Chenu and Morel (1905), that the parathyroids contain practically no iodin. Estes and Cecil maintain, therefore, that iodin as a constituent of the parathyroids may, generally speaking, be neglected and that if iodin is present it is in such minute quantities as to be of no functional significance.

In 1903 MacCallum attempted to make a specific cytolitic serum for the treatment of parathyroid tetany, but with no success. Parhon and Urechie (1907) and MacCallum and Voegtlin (1908) discovered practically simultaneously the palliative effect of calcium in parathyroid tetany. MacCallum and Voegtlin formulated the hypothesis that the parathyroids control in some way calcium metabolism and showed that a 5 per cent solution of calcium acetate or lactate either intravenously or by mouth controls parathyroid tetany; magnesium salts have a somewhat similar effect, but they are not so satisfactory on account of their toxic action; on the other hand, injections of potassium salts intensify all the symptoms which in turn can be ameliorated by the injection of calcium. In 1909 MacCallum and Voegtlin showed that there is a marked reduction in the calcium content of the tissues, especially of the blood and brain, during tetany, accompanied by an increased output of calcium and nitrogen, and that there is an increased output of ammonia with an increased ammonia ratio and an increase in the amount of ammonia in the blood. They confirmed their earlier work concerning the relief of tetany in animals and in man by the administration of calcium.

Carlson and Jacobson (1910) called attention to the striking similarity, if not identity, in the tetany symptoms of thyroparathyroidectomy, the symptoms of ammonia poisoning, and the symptoms of poisoning in Eck fistula dogs if fed on meat. They found that the ammonia-destroying power of the livers of tetanic animals was markedly depressed, leading to an increased percentage of ammonia in the blood. On further experimentation, however, they found (1911) the ammonia content of the blood to be normal and that intravenous injections of calcium did not alter the ammonia concentration, but did control the tetany; calcium salts had a less inhibitory action in ammonia poisoning than in parathyroid tetany. They found that calcium and strontium salts control equally well parathyroid tetany; that they act rapidly in the earlier and milder forms, but in the later stages there is little beneficial action; that the tetany, unless extreme, is suppressed also by an extract of hypophysis and by a hypertonic solution of sugar. Edmunds (1911) confirmed the value of calcium in controlling parathyroid tetany

but found no similar effect from pituitary extract; he obtained (1913) the best results from feeding milk to which calcium lactate had been added; and as a result of sugar tolerance tests Edmunds concluded that the thyroid gland hinders the assimilation of sugar and that the parathyroids favor it. MacCallum and Vogel (1913) confirmed, by direct analysis, that the blood of an animal in tetany, compared with that of a normal animal, is very poor in calcium; the administration of parathyroid extract did not increase the calcium. Marine (1913) believed that the parathyroids of birds are more susceptible to overgrowth than those of mammals and that calcium prevents such overgrowth. The cross-circulation experiments of MacCallum (1911) and of MacCallum and Vogel (1913) support the theory that the hyperexcitability of the nervous system is peripheral and is dependent upon some change in the character of the blood. MacCallum, Lambert and Vogel (1914), by removing calcium by dialysis from normal blood and passing this blood through an isolated extremity, produced an extreme hyperexcitability of the nerves quite like that observed in tetany; two animals with parathyroid tetany were bled and in one the blood was replaced by normal blood and in the other with dialyzed blood poor in calcium (otherwise normal); the symptoms were relieved in the first but not in the second animal. Marine (1914) also showed that calcium salts have a striking palliative effect on parathyroid tetany and suggested their use as a biologic test for the determination of the presence of accessory parathyroid tissue: in the absence of all parathyroid tissue calcium salts will not save the animal's life, while in the presence of active parathyroid tissue calcium is very effective. Howland and Marriott (1918), using their micromethod (1917), found that the calcium in the serum of normal persons varies between 9.2 mg. and 11.3 mg. or about 10 mg. for each 100 c.c. of serum. In the serum of patients with rickets they found from 7.9 mg. to 10.9 mg.; a majority showed a reduction of only 1 mg. (10 per cent) and a few were reduced by 2 mg. (20 per cent). In contrast, the calcium in the serum of patients in tetany of idiopathic origin was reduced from 3.5 mg. to 7.3 mg. or an average of 5.6 mg. for each 100 c.c.; of the eighteen patients studied all but one had less than 7 mg., more than a 40 per cent reduction.

They conclude that convulsions may be expected when the calcium content of the serum becomes less than 7.0 mg. for each 100 c.c., and they consider the results strikingly similar to those found by MacCallum and Vogel (1913) after parathyroidectomy; Binger (1917) also obtained similar results. However, Howland and Marriott do not consider the reduction of calcium as the only factor in tetany because Binger found the calcium much reduced in certain cases of nephritis and because they also observed three cases of tetany following the intravenous injection of sodium bicarbonate for the acidosis of diarrhea. They found no apparent alteration in tetany in the phosphate or magnesium content of the blood.

Greenwald (1911) made a detailed study of the urine in six dogs before and after parathyroidectomy and found that the excretion of nitrogen is increased only after the appearance of tetany; the ratio of urea nitrogen to total nitrogen is decreased; the proportion of the total urinary nitrogen excreted in the form of ammonia is increased very little if at all; the concentration of ammonia in the blood is not increased; the excretion of creatinin remains about the same or is slightly diminished; the creatin, purin nitrogen and undetermined nitrogen are increased; the excretion of sulfur, especialy inorganic sulfate and neutral sulfur, is increased, and finally phosphorus is retained in the first few days and later excreted in increased amounts. In later experiments Greenwald (1913) found a marked diminution in the excretion of phosphorus in urine after parathyroidectomy, resulting in its retention in the body, but no retention of sodium or potassium. He also showed (1916) that inosinic acid is not the toxic agent in parathyroid tetany.

Hunter (1914) found in sheep following removal first of the thyroid and later of the parathyroids that during a fast more nitrogen and more purin derivatives are excreted than normal; that the urine is alkaline and that the excretion of creatin is in excess of the excretion of creatinin and that there is a high sugar tolerance; the animals succumbed to inanition. Urechia (1914) did not find a constant increase in nitrogen in the blood and urine of animals in tetany.

Underhill and Blatherwick (1914) found that in tetany, following thyroparathyroidectomy, glycogen entirely disappears

from the liver and that the blood sugar content is markedly lowered.

Koch (1912 and 1913) reported finding methyl guanidin in the urine of dogs after parathyroidectomy; he also showed that digested proteins taken into the body have very toxic effects; he suggested that the parathyroid secretion is concerned with the anabolic process closely related to the building of nucleins. In later experiments, however, Koch (1915) isolated from the urine of parathyroidectomized animals methylcyanamid and trimethylamin and concluded that somewhere in the body methylcyanamid is generated and after parathyroidectomy accumulates to toxic quantities and causes death. Paton, Findlay and Burns (1915) showed that the injection of guanidin or methylguanidin apparently produces all of the characteristic symptoms of tetany in rats.

Wilson, Stearns and Janney (1915) showed that the intravenous injection of M/3.7 or M/7 hydrochloric acid solution relieves parathyroid tetany in dogs; the hydrochloric acid was less harmful if introduced in salt solution instead of water; the usual dose was 50 to 90 c.c. of M/3.7 hydrochloric acid in M/7 sodium chlorid solution. Sodium chlorid solution (M/7) if given without hydrochloric acid, produced no effect while some of the dogs were benefited by the oral administration of hydrochloric acid. Wilson, Stearns and Janney's conclusion that the relief of parathyroid tetany by the administration of acids suggests the possibility of a beneficial action due to a variation in the acid-base equilibrium in the body and offers a new point of view for the study of this and allied conditions.

Wilson, Stearns and Thurlow (1915) studied the values of the dissociation constant (Barcroft's K) of oxyhemoglobin, the alveolar air carbon dioxid tension, and the hydrogen-ion concentration of the blood of dogs after parathyroidectomy. They found that a condition of alkalosis may develop which is neutralized by acid products formed by muscular activity incident to tetany. A condition of acidosis may result after periods of acute tetany. Periodic variations in the "nonvolatile" acid-base equilibrium seem to accompany the periodic attacks. The condition of acidosis resulting from acute tetany or the injection of acid is associated with the relief from tetany. Calcium salts,

when injected into animals in tetany, lower the value of the dissociation constant of oxyhemoglobin and the alveolar carbon dioxid tension which is an effect similar to that brought about by the introduction of acids. The second paper by Wilson, Stearns and Janney (1915) shows that after parathyroidectomy in dogs there is usually a sudden diminution in the excretion of acids and ammonia and a decrease in the ammonia ratio and the hydrogen-ion concentration of the urine. With the development of tetany, the elimination of acids and ammonia increases and the values of the ammonia ratio and the hydrogen-ion concentration of the urine are increased. The variations may indicate that a condition of alkalosis results after parathyroidectomy but is neutralized by the tetany which develops. After acute or chronic tetany, an acidosis may occur.

Peterson, Jobling and Eggstein (1916) found that the onset of tetany following parathyroidectomy bears no constant relation to the ferment-anti-ferment balance of the serum.

Binger (1917) found that a solution of orthophosphoric acid or its sodium salts injected intravenously in dogs causes a diminution in the amount of calcium in the serum. The degree of diminution in the calcium content of the serum depends on the amount of phosphates introduced. When the phosphate solution is injected in amounts equivalent to 150 mg. phosphorus to the kilogram the serum calcium drops from its normal level of 10 mg. for each 100 c.c. to approximately 6 mg. At this level a condition of tetany supervenes, provided the neutral or alkaline salts have been injected. With the injection of acid phosphate solution, the calcium drop occurs unaccompanied by tetany. The phosphate solution becomes toxic when injected in the doses noted above in the neighborhood of pH 6.0. Therefore, Binger concluded that orthophosphates of sodium, if injected in sufficient quantity and at the right reaction, are toxic and produce tetany in dogs; that the toxicity is due to a specific action of the phosphate ions in combination with the reaction of the solution in which they exist; and that the tetanic condition caused by phosphates is intimately associated with a decrease in calcium in the serum, but it is not dependent on this alone since a drop in calcium may occur without the appearance of tetany.

McCann (1918) found that after parathyroidectomy there is a marked increase in the carbon dioxid combining power of the blood plasma, coincident with the development of tetany. Following an operation on the stomach which excludes the acid secreted from the duodenum tetany develops and is accompanied by an increase in the carbon dioxid combining power of the plasma similar to that of parathyroid tetany. Brown, MacLachlan and Simpson (1920) report constitutional reactions following the intravenous injection of 1.25 gm. calcium lactate; the reaction varies between slight drowsiness and collapse and lasts from one to seven hours.

Grant and Goldman (1920) by forced breathing for from fifteen to sixty minutes, produced tetany in themselves; the symptoms included carpopedal spasm, Chvostek's, Trousseau's and Erb's signs, and in one instance, a tetanic convulsion. As a result of the fall of alveolar carbon dioxid tension produced by over-ventilation there is a reduction in the hydrogen-ion concentration of the blood, a reduction of the carbon dioxid capacity of the plasma, a change in the reaction of the urine to the alkaline side, a decreased excretion of ammonia, and a slight increase in the calcium content of the serum. Grant and Goldman believe that the underlying factor in the tetany of forced respiration is the alkalosis.

MacCallum, Lintz, Vermilye, Leggett and Boas (1920) report a peculiar condition accompanied by convulsions occurring whenever the pylorus is obstructed so that the acid gastric juice is all removed and no chlorids are given in the food; they point out, however, that the condition is not the same as that produced by parathyroidectomy. The muscular rigidity with vibrating chronic twitchings and extreme tachypnea are lacking; the animals are apathetic until seized by violent general convulsion followed by a kind of coma; electrical excitability increases, but not as in parathyroid tetany. The introduction of the chlorin ion as hydrochloric acid has no benefit, whereas the administration of sodium chlorid continuously prevents the development of changes in the electrical excitability and disturbances of the alkali reserves. Calcium lactate, although it exerts a temporary effect, has no controlling influence as in parathyroid tetany. Symptoms similar to those caused by the removal of chlorids

are produced by the injection of sodium carbonate or sodium bicarbonate solution.

Following the finding of methyl guanidin in the urine by Koch (1912) and the discovery by Paton, Findlay and Burns (1915) that both guanidin and methyl-guandin cause characteristic symptoms of tetany in rats, Paton and Findlay with Watson, Burns, Sharpe and Wishart presented a series of papers in 1916 which aimed to show the etiology of tetany and its relationship to guanidin and methyl-guanidin intoxication. Their main conclusions were that the symptoms of tetany are due to some change in the nerve cells of the cord, and that the increased excitability of the neuro-myon is caused by an action on the nerve endings. As a result of an extensive comparison of the symptomatology of idiopathic tetany, postoperative tetany in man, *tetania parathyreopriva,* and guanidin poisoning, they concluded that all these conditions are of the same nature and that the first three are due to the development of guanidin in the body as the result of some interference with the action of the parathyroids which normally control guanidin metabolism and by so doing probably influence the tone of muscles. They believe, therefore, that in man there is a close association between idiopathic tetany and the tetany following removal of the parathyroids and that in both the symptoms are due to an increase of guanidin in the body. Paton and Findlay found a marked increase in the amount of guanidin and methyl-guanidin in the blood and urine of dogs after the removal of the parathyroids and in the urine of children suffering from idiopathic tetany. They do not believe the symptoms of tetany to be due primarily to a decrease in any constituent of the blood such as calcium ions nor to an increase in ammonia or xanthin or B-iminazolyl-ethylamin in the blood. They do not consider that an increased electrical excitability can be taken as a measure of the severity of the condition. Although they believe their experiments show that *tetania parathyreopriva* and idiopathic tetany are identical they admit that the histologic evidence for their implication in the latter condition is not conclusive. Burns and Watson (1918) further showed that guanidin intoxication and parathyroid tetany produce an interference with the vago-cardiac inhibition which is removed by salts of calcium.

Guanidin has first a nicotin action, poisoning the synapsis; after more extensive application it has an atropin action, causing paralysis of the terminal ganglia in the heart of the frog. Guanidin does not paralyze the sympathetic (accelerator) mechanism in the heart. Henderson (1918) found that after parathyroidectomy there is a fall in the total guanidin and in the free guanidin of muscle and a rise in the creatin both absolutely and in relation to the total nitrogen. The fall in the free guanidin-nitrogen corresponds fairly closely to the rise in the creatin nitrogen and may indicate a synthesis of part of this nitrogen. The fall in the total guanidin is far in excess of the nitrogen in free guanidin and in creatin and must indicate either a liberation of guanidin from the muscle or a failure in the power of the muscle to take up guanidin formed elsewhere, either of which conditions may be correlated with the increase in the blood and the urine already demonstrated by Burns and Sharp (1916).

Pavloff (1913) reported in the publications of the University of Cracow an article on the exchange of gases and metabolism in different diets after removal of the parathyroid glands; this publication has been inaccessible. Löffler (1919) reports no change in the basal metabolism in a case of *tetania parathyreopriva.*

IV. IDIOPATHIC TETANY

Hertz (1913) gives a case report describing symptoms which, he believes, might be attributable to idiopathic parathyroid insufficiency; marked improvement followed the administration of Armour's ox parathyroid. In view of the general experience of negative results from parathyroid medication and because of the doubtful evidence in this patient of parathyroid disease too much stress should not be laid on this isolated report. Morris (1915) reported the case of a patient in Halsted's clinic who had taken 3 gr. of powdered parathyroid extract (Armour) daily for eighteen months; when the patient was first seen he was in a deplorable mental condition, nervous and helpless, urinating and defecating in bed. A very prompt improvement occurred when use of the extract was discontinued.

Mann and Thiemich simultaneously (1900) reported cathodal hyperexcitability in infantile tetany. Wilcox (1911) studied the electrical hyperirritability in its relation to the parathyroid glands and found it increased and therefore considered it a diagnostic help in latent or developing tetany. Holmes (1916) reviewed the evidence of the reliability of the electrical diagnosis of tetany and concluded that the appearance of cathodal opening contractions under 5 ma. is pathognomic in children less than five years of age. Howland and Marriott (1918) found a low calcium content with unmistakable symptoms of tetany, thus confirming the specificity of the cathodal hyperexcitability as a diagnostic method. The anodal hyperexcitability of von Pirquet is less positive, although usually accompanied by a slight decrease of calcium, but it may occur in perfectly normal infants as shown by Holmes (1916).

Falta (1915) defines tetany as an "abnormally increased condition of excitement of the nervous system, that is demonstrable in a heightened excitability of the motor, sensible, sensory and vegetative nerves, and under certain circumstances, in paresthesias, and bilateral intermittent, for the most part painful spasms, with intact consciousness, or becomes manifest through phenomena of irritation on the part of the vegetative nerves; to the picture of tetany belong also trophic and certain metabolic disturbances; the manifestations are the result of an insufficiency of the parathyroid glands."

An excellent review is given by Falta of the symptomatology and diagnosis, especially the electrical reactions, of the various forms of tetany in infants, children, and adults, including gastro-intestinal and occupational tetany and tetany during pregnancy and lactation. All of these conditions he attributes to insufficiency of the parathyroid glands and ably presents the few facts and many arguments in favor of this view. In the preceding pages we have cited the experimental evidence, but we refer the reader to Falta for a presentation of the clinical and theoretic considerations with the literature supporting the hypothesis of an underlying parathyroid insufficiency in these various tetanic conditions.

V. CLINICAL SYMPTOMS AND TREATMENT OF PARATHYROID TETANY

Clinically parathyroid tetany may occur after operations on the thyroid gland, due either to the complete removal of all or of the greater part of the parathyroid tissue or to an injury of the parathyroids or their blood supply by the operative procedures. The onset of symptoms is usually two to three days after the operation but it may be sooner or later. There may be prodromal symptoms such as headache and general weakness, accompanied by radiating pains downs the extremities, especially the upper, and chronic twitchings. The diagnosis is usually not evident until definite spasms occur; they are almost always symmetrical and bilateral. As a rule the hand is most often affected and the patient presents a characteristic contraction spoken of as the "accouchers" hand, which consists in flexion of the fingers at the metacarpal phalangeal joint with adduction of the thumb; sometimes the thumb is completely adducted and tightly clasped by the flexed second and third fingers together with flexion of the wrist and less often flexion of the forearm. Rarely are there intercurrent contractures of the muscles of the face or trunk. Erb (1874) pointed out that in tetany (not only parathyroid tetany but other forms as well) the electric excitability of the motor nerves is increased; Trousseau (1851) showed that during intervals between spasms attacks could be brought on by compression of the main nerve trunk; Chvostek (1907) found that the facial muscles can be made to twitch by tapping along the course of the facial nerve; Pool (1907) and Schlesinger (1910) demonstrated that contractures can be elicited in the lower extremities by putting the sciatic nerve on the stretch by extreme flexion of the thigh and leg on the trunk.

The results obtained from treatment with parathyroid extract or by parathyroid transplantation have on the whole proved disappointing, and the best clinical results have been obtained from the administration of calcium. In parathyroid tetany following the modern operations on the thyroid and when in all probability the parathyroid tissue is not entirely destroyed, the spasms can usually be controlled promptly by the administration either orally or intravenously of calcium lactate. As soon as the tetany becomes evident, 40 to 60 gr. of calcium

lactate should be given every two to four hours until the tetany is controlled, when smaller doses will usually be found sufficient. With some patients the calcium may be omitted after a few days, while with others it is necessary to continue its administration either intermittently or regularly for a prolonged period.

VI. SUMMARY

Our knowledge regarding the function of the parathyroid glands may be summarized as follows:

1. In many species of animals the removal of all parathyroid tissue causes death from tetany, within a few days in most instances; the herbivora are less liable to tetany than the carnivora; age appears to have a definite influence on its frequency and severity as probably also do pregnancy and lactation. There is some evidence of late trophic changes in those animals that survive parathyroidectomy and have few or no tetanic symptoms.

2. The preservation of very small amounts of parathyroid tissue prevents or renders the tetany less intense.

3. From the evidence at hand, the function of the parathyroids appears to be distinct and separate from that of the thyroid; their only relationship seems to be anatomic and not functional; the parathyroids are not embryonic thyroid tissue.

4. There is evidence that their function is in some way concerned with calcium or guanidin metabolism or with both; they may play some part in the regulation or maintenance of the acid-base equilibrium in the body.

5. The experimental evidence pointing to the parathyroids as the primary cause of idiopathic tetany, unassociated with operative procedures on the thyroid, is very limited.

6. The only definite clinical entity which has yet been proved experimentally to be of parathyroid origin is the tetany occasionally seen after operations on the thyroid. In these conditions calcium in large doses usually ameliorates the symptoms. The reports as to the benefit obtained by parathyroid transplantation or feeding are not convincing.

BIBLIOGRAPHY

(References which have an asterisk before them are referred to in the text)

1851

*Remak, R.: Untersuchungen über die Entwickelung des Wirbelthieres. Berlin, Reimer, 1851, **25,** 194.

*Trousseau: Quoted by Pool (1915).

1864

*Virchow, R.: Die krankhaften Geschwülste. Berlin, Hirschwald. 1863-1867, **3,** 13.

1874

*Erb: Quoted by Pool (1915).

1879

*Wölfler, A.: Die Aortendrüse und der Aortenkropf. Eine vorläufige Mittheilung. Wien. med. Wchnschr., 1897, **5,** 198.

1880

*Sandström, I.: Ueber eine neue Drüse beim Menschen und bei verschiedenen Säugethieren. Upsala läkaref. förh., 1880, **15,** 441-471; Hofmann and Schwalbe's Jahresb., Upsala, 1881, **9,** 114-118.

*Wölfler, A.: Ueber die Entwickelung und den Bau der Schilddrüse mit Rücksicht auf die Entwickelung der Kröpfe. Berlin, 1880.

1881

*Baber, E. C.: Researches on the minute structure of the thyroid gland. Abst. Proc. Roy. Soc. London, 1880-1881, **31,** 279-282.

*Stieda, L.: Untersuchungen über die Entwickelung der Glandula thymus, Glandula thyroidea und Glandula carotica. Leipzig, Engelmann, 1881, 38 p.

*Weiss, N.: Ueber Tetanie. Volkmann's Samml. klin. Vortr. Leipzig., 1881, No. 189, 1675-1704.

1883

*Wölfler, A.: Ueber die Entwickelung und den Bau des Kropfes. Arch. f. klin. Chir., 1883, **29,** 1-97; 755-866.

1884

*Schiff: Bericht über eine Versuchsreihe betreffend die Wirkungen der Exstirpation der Schilddrüse. Rev. méd. de la Suisse Rom., Geneva, 1884, **4,** 66, 438.

*Wagner, J.: Ueber die Folgen der Exstirpation der Schilddrüse nach Versuchen an Tiren. Wien. med. Bl., 1884, **7,** 771-775.

1886

Fuhr, F.: Die Exstirpation der Schilddrüse. Eine experimentelle Studie. Arch. f. exper. Path. u. Pharmakol., Leipzig, 1886, **21,** 387-460.

*Horsley, V.: The pathology of the thyroid gland. Lancet, Lond., 1886, **2,** 1163-1164.

1887

*Maurer: Quoted by Kohn, 1895.

1888

*Carle, A.: Ueber die Exstirpation der Schilddrüse. Centralbl. f. Physiol., Leipzig, 1888-89, **2,** 213-218.

*Rogowitch, N.: Sur les effets de l'ablation du corps thyroide chez les animaux. Arch. de physiol. norm. et path., Par., 1888, 4.s., **2,** 419-467.

1890

*v. Eiselsberg, A.: Ueber Tetanie im Anschluss an Kropfoperationen. Wien. 1890, Hölder, 1890, 37 p.

1891

*Gley, E.: Note sur les fonctions de la glande thyroide. Compt. rend. Soc. de biol., Par., 1891, **3,** 250; 567; 583.
Sur la toxicité des urines des chiens thyroidectomisés; contribution à l'étude des fonctions du corps thyroide. Compt. rend. Soc. de biol., Par., 1891, **3,** 366-368.
Sur les effets de l'extirpation du corps thyroide. Compt. rend. Soc. de biol., Par., 1891, **3,** 551-554.
Sur les fonctions du corps thyroide. Compt. rend. Soc. de biol., Par., 1891, **3,** 841-842.
Sur les fonctions de la glande thyroide chez le lapin et chez le chien. Compt. rend. Soc. de biol., Par., 1891, **3,** 843-847.

*Laulanié: Sur la toxicité urinaire après la thyroidectomie double chez le chien. Compt. rend. Soc. de biol., Par., 1891, **3,** 308-312.

1892

*Cristiani, H.: Sur les glandules thyroidiennes chez le rat. Compt. rend. Soc. de biol., Par., 1892, 9.s., **4,** 798-799.

v. Eiselsberg, A.: Ueber erfolgreiche Einheilung der Katzenschilddrüse in die Bauchdecke und Auftreten von Tetanie nach deren Exstirpation. Wien. klin. Wchnschr., 1892, **5,** 81-85.

*Gley, E.: Effets de la thyroidectomie chez le lapin. Arch. de physiol. norm. et path., Par., 1892, **4**, 135-147.
Recherches sur la fonction de la glande thyroide. Arch. de physiol. norm. et path., Par., 1892, **4**, 311-326.
Action du bromure de potassium sur les chiens thyroidectomisés. Compt. rend. Soc. de biol., Par., 1892, **4**, 300-302.
Des troubles tardifs consécutifs à la thyroidectomie chez le lapin. Compt. rend. Soc. de biol., Par., 1892, **4**, 666-669.
Des effets de la thyroidectomie; remarques sur la communication de M. Moussu. Compt. rend. Soc. de biol., Par., 1892, 9.s., **4**, 979-981; 1000-1003.

*Hofmeister: Zur Physiologie der Schilddrüse. Fortsch. d. Med., Berlin, 1892, **10**, 81-87; 121-130.

*Moussu, G.: Effets de la thyroidectomie chez nos animaux domestiques. Compt. rend. Soc. de biol., Par., 1892, **4**, 271-276.
Cretinisme expérimental sous les deux formes typiques. Compt. rend. Soc. de biol., Par., 1892, **4**, 972-979.

1893

*Chantemesse & Marie, R.: Les glandes parathyroidiennes de l'homme. Bull. et mém. Soc. méd. d. hôp. de Par., 1893, 3.s., **10**, 202-204.

*Cristiani, H.: Des glandules thyroidiennes accessoires chez la souris et le campagnol. Arch. de physiol. norm. et path., Par., 1893, 5.s., **5**, 279-284.
Nouvelles recherches sur les organes thyroidiennes des rongeurs. Compt. rend. Soc. de biol., Par., 1893, **5**, 4-5.
De la thyroidectomie chez le rat pour servir à la physiologie de la glande thyroide. Arch. de physiol. norm. et path., Par., 1893, 5.s., **5**, 39-46.
Remarques sur l'anatomie et la physiologie des glandes et glandules thyroidiennes chez le rat. Arch. de physiol. norm. et path., Par., 1893, **5**, 164-168.

*Gley, E.: Glande et glandules thyroides du chien. Compt. rend. Soc. de biol., Par., 1893, **5**, 217.
Nouvelle preuve de l'importance fonctionnelle des glandules thyroïdes. Compt. rend. Soc. de biol., Par., 1893, **5**, 396-400.
Sur la polypnée des chiens thyroidectomisés. Compt. rend. Soc. de biol., Par., 1893, **5**, 515.

*Marfori, P.: Ueber die Ammoniakmengen, welche der Organismus in Harnstoff umzuwandeln vermag. Arch. f. exper. Path. u. Pharmakol., Liepz., 1893-94, **33**, 71-78.

*Moussu, G.: Sur la fonction thyroïdienne. Compt. rend. Soc. de biol., Par., 1893, **5**, 280-283; 394-395.
Sur la fonction thyroïdienne, crétinisme expérimental sous ses deux formes typiques. Compt. rend. Soc. de biol., Par., 1893, **4**, 972-979.

*Nicolas, A.: Glande et glandules thyroides (parathyroides) chez les chéiroptères. Bull. des séances de la Soc. d. Sc. de Nancy, 1893, **5**, quoted by Biedl, 1913.

1894

*Hürthle, K.: Beiträge zur Kenntniss des Secretionsvorgangs in der Schilddrüse. Arch. f. d. ges Physiol., Bonn, 1894, **56**, 1-44.

*Laulanié: Sur la toxicité urinaire apres la thyroidectomie double chez le chien. Compt. rend. Soc. de biol., Par., 1894, 10. s., **5**, 187-189.

Prenant: Quoted by Dock, 1915.

*Verstraeten, C. & Vanderlinden, O.: Étude sur les fonctions du corps thyroide. Mém. couron. de l'Acad. roy. de méd. de Belg. 1894, **13**, pp.?

*Zerlinska, M.: Beiträge zur Kenntniss der normalen und strumösen Schilddrüse des Menschen und des Hundes. Virchow's Arch. f. path., Anat. [etc.], Berl., 1894, **136**, 170-194.

1895

*Gley, E. & Nicolas, A.: Premiers résultats de recherches sur les modifications histologiques des glandules thyroidiennes après la thyroidectomie. Compt. rend. Soc. de biol., Par., 1895, 216-218.

*Kohn, A.: Studien über die Schilddrüse. Arch. f. mikr. Anat., Bonn, 1894-95, **44**, 366-422.

Oliver, G. & Schäfer, E. A.: On the physiological action of extracts of pituitary body and certain other glandular organs. J. Physiol., Lond., 1895, **18**, 277-279.

Schaper, A.: Ueber die sogenannten Epithelkörper (Glandulae parathyroideae) in der seitlichen Nachbarschaft der Schilddrüse und der Umgebung der Arteria carotis der Säuger und des Menschen. Arch. f. mikr. Anat., Bonn, 1895, **46**, 239-279.

1896
*Blumreich, L. & Jacoby, M.: Experimentelle Untersuchungen über die Bedeutung der Schilddrüse und ihrer Nebendrüsen für den Organismus. Arch. f. d. ges. Physiol., Bonn, 1896, **64**, 1-52.
*Groschuff, K.: Bemerkungen zu der vorläufigen Mitteilung von Jacoby: Ueber die Entwickelung der Nebendrüsen der Schilddrüse und der Carotidendrüse. Anat. Anz., Jena, 1896, **12**, 497-512.
Jacoby, M.: Ueber die Entwickelung der Nebendrüsen der Schilddrüse und der Carotidendrüse. Anat. Anz., Jena, 1896, **12**, 152-157.
Vassale, G. & Donaggio, A.: Le alterazioni del midollo spinale nei cani operati di estirpazione delle ghiandole paratiroiuee. Riv. spor. di freniat., 1896, **22**, 853-857.
*Vassale, G. & Generali, F.: Sur les effets de l'extirpation des glandes Parathyroidiennes. Arch. ital. de biol., Pisa, 1896, **26**, 61-65.
Sugli effetti dell' estirpazione delle ghiandole paratiroidee. Riv. di patol. nerv. e ment., Firenze, 1896, **1**, 95.
Sur les effets de l'extirpation des glandes parathyreoidiennes. Arch. ital., de biol., Par., 1896, **26**, 61-65.
Sur les effets de l'extirpation des glandes parathyreoides. Arch. ital. de biol., Par., 1896, **25**, 459-464.
*Verdun, P.: Sur les glandules satellites de la thyroide du chat et les kystes qui en derivent. Compt. rend. Soc. de biol., Par., 1896, **3**, 899-901.
1897
Cristiani, H. & Ferrari, E.: De la nature des glandules parathyroidiennes. Compt. rend. Soc. de biol., Par., 1897, 10.s., **4**, 885.
*Gley, E.: Sur la fonction des glandules parathyroides: remarques à propos de la communication de M. Moussu. Compt. rend. Soc. de biol., Par., 1897, 10.s., **4**, 46-47.
Bemerkungen über die Funktion der Schilddrüse und ihrer Nebendrüsen. Arch. f. d. ges. Physiol., Bonn, 1897, **66**, 308-319.
*Moussu, G.: Fonction parathyroidienne. Compt. rend. Soc. de biol., Par., 1897, 10.s., **4**, 44-46.
Recherches sur les fonctions thyroidiennes et parathyroidiennes. Thèse de Paris, 1897.
Tourneux, F. & Verdun, P.: Sur les premiers développments de la thyroide, du thymus et des glandules parathyroidiennes chez l'homme. Jour. de l'anat. et de la physiol., Par., 1897, **33**, 305-325.
*Vassale, G. & Donaggio, A.: Les alterations de la moelle épinière chez les chiens opérés d'extirpation des glandes parathyreoidiennes. Arch. ital. de biol., Pisa, 1897, **27**, 124-128.
*Vassale, G. & Generali, F.: Intorno agli effetti dell' estirpazione delle ghiandole paratiroidee. Riforma med., Napoli, 1897, **1**, 800.
L'alimentazione tiroidea contro gli effetti dell' estirpazione della ghiandole paratiroidee. Riforma med., Napoli, 1897, **2**, 235.
Sopra le ghiandole paratiroidee esterne dell' norma. Riforma med., Napoli, 1897, **2**, 631.
Ulteriori ricerche intorno all ghiandole paratiroidee. Riforma med., 1897, **3**, 77.
*Vassale, G.: Tetania d'allattamento in una cagna parzialmente paratiroidectomizzata. Riv. sper. du freniat., 1897, **23**, 915-924.
1898
Kürsteiner, W.: Die Epithelkörperchen des Menschen in ihrer Beziehung zur Thyroidea und Thymus. Anat. Hefte., Weisb., 1898, **11**, 391-459.
*Moussu, G.: Sur la fonction parathyroidienne. Compt. rend. Soc. de biol., Par., 1898, 10.s., **5**, 867-869.
*Vassale, G.: Tetanie provoquée par l'allaitement chez une chienne partiellement parathyreoidectomisée. Arch. ital. de biol., Torino, 1898, **30**, 49-59.
Tetania della gravidanza in sequito ad estirpazione parziale delle ghiandole paratiroidee. Riforma med., Napoli, 1898, **3**, 91-92; Boll. d. Soc. med.-chir., di Modena, 1898.
*Verdun: Contribution à l'étude des dérivés branchiaux. Thèse de Paris, 1898.
Welsh, D. A.: On the parathyroid glands of the cat: A preliminary study in experimental pathology. J. Path & Bacteriol., Cambridge, 1898, **5**, 202-220.
1899
Capobianco, F. & Mazziotti, L.: Sur les effets de la parathyroidectomie. Recherches microscopiques et experimentales. Arch. ital. d. biol., Torino, 1899, **31**, 472-473.
Le lesioni renali seguite alla paratiroidectomia. Arte med., 1900, **2**, 543-546.

1900
Kohn, A.: Die Epithelkörperchen. Anat. Hefte., Weisb., 1900, **10,** 194-252.
Loeb, J.: On ion-protein compounds and their rôle in the mechanics of life phenomena. I. The poisonous character of a pure NaCl solution. Am. J. Physiol., Boston, 1900, **3,** 327-338.
*Mann, L.: Untersuchungen über die electrische Erregbarkeit im frühen Kindesalter, mit besonderer Beziehung auf die Tetanie. Monatsch. f. Psychiat. u. Neurol., 1900, **7,** 143.
Mendel, L. B.: On the occurrence of iodine in the thymus and thyriod glands. Am. J. Physiol., Boston, 1900, **3,** 285-290.
*Vassale, G. & Generali, F.: Fonction parathyreoidienne et fonction thyreoidienne. Arch. ital. de biol., Torino, 1900, **33,** 154-156.
*Thiemich, M.: Ueber Tetanie und tetanoide Zustände im ersten Kindesalter. Jahrb. f. Kinderh., Leipz., 1900, **3,** F.i, 99-120.
1901
v. Cyon, E. & Oswald, A.: Ueber die physiologischen Wirkungen einiger aus der Schilddrüse gewonnener Producta. Arch. f. d. ges. Physiol., Bonn., 1901, **83,** 199-206.
v. Eiselsberg: Krankheiten de Schilddrüse. Deutsch. Chir., 1901, **38.**
*Gley, E.: The pathogeny of exopthalmic goiter. Brit. M. J., Lond., 1901, **ii,** 771-773.
Gregor, K.: Ueber Muskelspasmen und Muskelhypertonie im Säuglingsalter und ihre Abhängigkeit von der Ernährung. Monatschr. f. Psychiat. u. Neurol., 1901, **10,** 81-94.
*Sabbatani, L.: Funzione biologica del calcio. Revista sper. di freniat., 1901, **27,** 946.
1902
Benjamins, C. E.: Ueber die Glandulae parathyroideae (Epithelkörperchen). Beitr. z. path. anat. v. allg. Path., Jena, 1902, **31,** 143-182.
1903
Biedl, A.: Innere Sekretion. Wien. Klin., 1903, **29,** 281-338.
*Jeandelize: Insufficance thyreoidienne et parathyreoidienne. Paris, 1903. Quoted by Pool, 1907.
*MacCallum, W. G.: On the production of specific cytolytic sera for thyroid and parathyroid with observations on the physiology and pathology of the parathyroid gland, especially in its relation to exophthalmic goitre. Tr. Ass. Am. Phys., Phila., 1903, **18,** 35-53; Med. News, 1903, **83,** 820-826.
*Thiemich, M.: D l'état actuel de nos connaissance des convulsions chez les nourressons. Rev. d'hyg. et méd. inf., Par., 1903, **2,** 309-337.
1904
Ball, J. M.: Influence of resection of the cervical sympathetic in optic-nerve atrophy, hydrophthalmos and exophthalmic goiter. J. Am. M. Ass., 1904, Chicago, **42,** 287-290.
*Erdheim, J.: Beiträge zur pathologischen Anatomie der menschlichen Epithelkörperchen. Ztschr. f. Heilk., 1904, **25,** 1-15.
Kishi, K.: Beiträge zur Physiologie der Schilddrüse. Virchow's Arch. f. path. Anat. [etc.], Berl., 1904, **176,** 260-313.
*Vassale, G.: Le traitement de l'éclampsie gravidique par la parathyréoidine et considérations sur la physiopathologie des glandes parathyréoides. Arch. ital. de biol., Torino, 1905, **43,** 177-196.
1905
Camus, L.: Greffes parathyroidiennes chez l'animal normal et chez l'animal partiellement éthyroidé. Compt. rend. Soc. de biol., Par., 1905, **58,** 439-442.
*Chenu, J. & Morel, A.: Localisation de l'iode dans les glandules parathyroides externes. Compt. rend. Soc. de biol., Torino, 1904, **56,** 680-682.
Chvostek, F.: Bemerkungen zur Aetiologie der Tetanie. Wien. klin. Wschnschr., 1905, **18,** 969-974.
*MacCallum, W. G.: Parathyroid therapy and the relation of the parathyroid gland to exophthalmic goiter. Am. Med., Burlington, Vt., 1905, **9,** 934; Med. News, 1905, **86,** 625.
Die Beziehung der Parathyroiddrüsen zu Tetanie. Centralbl. f. allg. Path. u. path. Anat., Jena, 1905, **16,** 385-387.
Pineles, F.: Klinische und experimentelle Beiträge zur Physiologie der Schilddrüse und der Epithelkörperchen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, 1905, **14,** 120-156.
*Quest, R.: Ueber den Kalkgehalt des Säuglingsgehirn und seine Bedeutung. Jahrb. f. Kinderh., Leipz., 1905, **11,** 114-121.
*Vincent, S. & Jolly, W. A.: Some observations upon the functions of the thyroid and parathyroid glands. J. Physiol., Lond., 1905, **32,** 65-86.

Walsh, J. J.: Graves' disease and parathyroid therapy. Am. Med., 1905, **9**, 815.

1906

Adler & Thaler: Ueber Tetania parathyreopriva. Wien. klin. Wchnschr., 1906, **19**, 779-780.

Blum, F.: Neues zur Physiologie und Pathologie der Schilddrüse. München med., Wchnschr., 1906, **53**, 890, 891.

*v. Cybulski, I.: Ueber den Kalkstoffwechsel des tetaniekranken Säuglings. Monatschr. f. Kinderh., Leipz. & Wien., 1906, **5**, 409-413.

*v. Eiselsberg, A.: Tetania parathyreopriva. Wien. klin. Wchnschr., 1906, **19**, 780-782.

*Erdheim, J.: Ueber Tetania parathyreopriva. Wien. klin. Wchnschr., 1906, **19**, 716-717.

Tetania parathyreopriva. Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, 1906, **16**, 632-744.

v. Frankl-Hochwart, L.: Die Prognose der Tetanie der Erwachsenen. Neurol. Centralbl., Leipz., 1906, **25**, 642.

*Kocher: Cachexia thyreopriva. Tetania thyreopriva. Basedowsche Krankheit. München. med. Wchnschr., 1906, **53**, 889.

*MacCallum, W. G.: The surgical relations of the parathyroid glands. Brit. M. J., Lond., 1906, **2**, 1282-1286.

Park, R.: What do recent studies regarding the thyroid and parathyroid teach concerning the treatment of exophthalmic goiter? Med. Rev. of Rev., N. Y., 1906, **12**, 595-606.

Pineles, F.: Zur Pathogenese der Tetanie. Deutsch. Arch. f. klin. Med., Berl., 1906, **85**, 491-524.

*Stoeltzner, W.: Die Kinder-Tetanie (Spasmophilie) als Calciumvergiftung. Jahrb. f. Kinderh., Leipz., 1906, **63**, 661-683.

*Vassale, G.: Éclampsie gravidique et insuffisancé parathyréoidienne. Arch. ital. de biol., Torino, 1906-07, **46**, 143.

1907

Beebe, S. P.: The physiology of the thyroid gland in its relation to exophthalmic goiter. J. Am. M. Ass., Chicago, 1907, **49**, 1155-1158.

Chvostek, F.: I. Die mechanische Uebererregbarkeit der motorischen Nerven bei Tetanie und ihre Beziehung zu den Epithelkörpern. Wien. klin. Wchnschr., 1907, **20**, 487-493. II. Das kausale und die auslosenden Momente. Der akute Anfall von Tetanie nach Tuberkulininjektion. Ibid., 625-632. III. Die elektrische Uebererregbarkeit der motorischen Nerven. Ibid., 787-792.

*Cohn, M.: Kalk, Phosphor und Stickstoff im Kindergehirn. Deutsch. med. Wchnschr., Berl., 1907, **33**, 1987-1991.

*Estes, W. L., Jr. & Cecil, A. B.: The relation of iodine to the parathyroid. Johns Hopkins Hosp. Bull., Balt., 1907, **18**, 331-332.

The parathyroid of the horse. Johns Hopkins Hosp. Bull., Balt., 1907, **18**, 335-337.

Forsyth, D.: The parathyroid glands in man. Tr. Path. Soc., Lond., 1907, **58**, 154-177.

v. Frankl-Hochwart, L.: Die Tetanie der Erwachsenen. Wien. Hölder, 2 ed., 1907, 148 pp.

*Getzowa, S.: Ueber die Glandula parathyreoidea, intrathyreoideale Zellhaufen der selben und Reste des postbranchialen Körpers. Virchow's Arch. f. path. Anat. [etc.], Berl., 1907, **188**, 181-235.

*Halsted, W. S.: Hypoparathyreosis, status parathyreoprivus, and transplantation of the parathyroid gland. Am. J. Med. Sc., Phila., 1907, **134**, 1-12.

*Halsted, W. S. & Evans, H. M.: The parathyroid glandules. Their blood supply and their preservation in operation upon the thyroid gland. Ann. Surg., Phila., 1907, **46**, 489-506.

Kocher: Ueber Tetanusbehandlung. Cor.-Bl. f. schweiz. Aerzte, Basil, 1907, **37**, 381.

*MacCallum, W. G. & Fabyan, M.: On the anatomy of a myxoedematous idiot. Johns Hopkins Hosp. Bull., Balt., 1907, **18**, 341-345.

*MacCallum, W. G., Thomson, H. S. and Murphy, J. B.: Tetany after parathyroidectomy in herbivora. Johns Hopkins Hosp. Bull., Balt., 1907, **18**, 333-335.

*Parhon, C. & Urechie, C. S.: Untersuchungen über den Einfluss dem die Calcium und Sodiumsalze auf den Verlauf der experimentellen Tetanie ausüben. Neurol. Centralbl., Leipz., 1907, **26**, 1099.

Pfeiffer, H. & Mayer, O.: Ueber die funktionstüchtige Einheilung von transplantierten Epithelkörperchen des Hundes. Wien. klin. Wchnschr., 1907, **20**, 699-700.

*Pool, E. H.: Tetany parathyreopriva. Ann. Surg., Phila., 1907, **46**, 507-540.

Preble, R. B.: Medical treatment of exophthalmic goiter. J. Am. M. Ass., Chicago, 1907, **49**, 1238-1240.

v. Verebely, T.: Beiträge zur Pathologie der branchialen Epithelkörperchen. Virchow's Arch. f. path. Anat. [etc.], Berl., 1907, **187**, 80-105.

*Yanase, J.: Ueber Epithelkörperbefunde bie galvanischer Uebererregbarkeit der Kinder. Wien. klin. Wchnschr., 1907, **20**, 1157-1160.

1908

Branham, J. H.: Tetany following thyroidectomy cured by the subcutaneous injection of parathyroid emulsion. Ann. Surg., Phila., 1908, **48**, 16-164.

Edmunds, W.: The parathyroid glands. Lancet, Lond., 1908, **1**, 811.

v. Eiselsberg, A.: Ueber Vorkommen und Behandlung der Tetania parathyreopriva beim Menschen. Beitr. z. Physiol. u. Path., Festschr., L. Hermann, Stuttgart, 1908, 1-21.

*Forsyth, D.: The parathyroid glands. Quart. J. Med., Oxford., 1907-08, **1**, 150-172; 287-311.

The comparative anatomy, gross and minute, of the thyroid and parathyroid glands in mammals and birds. J. Anat. & Physiol., Lond., 1907-08, **43**, 141; 319.

Hagenbach, E.: Experimentelle Studie über die Funktion der Schilddruse und der Epithelkorperchen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena., 1908, **18**, 329-376.

*Islein, H.: Tetanie jugendlicher Ratten nach Parathyreoidektomie, Steigerung der tetanischen Reaktionsfähigheit jugendlichen Ratten bei Nachkommen parathyreoidektomierter Ratten. Deut. Ztschr. f. Chir., Leipz., 1908, **93**, 397-401.

Wachstumshemmung infolge von Parathyreoidektomie bei Ratten. Ein Beitrag zur Kenntnis der Epithelkörperchen-Funktion bei jungen Ratten. Deutsch. Ztschr. f. Chir., Leipz., 1908, **93**, 494-500.

*MacCallum, W. G.: The physiology and pathology of the parathyroid glands. Proc. Path. Soc., Phila., 1908, **11**, 115-128.

*MacCallum, W. G. & Voegtlin, C.: On the relation of the parathyroid to calcium metabolism and the nature of tetany. Johns Hopkins Hosp. Bull., Balt., 1908, **19**, 91-92.

Michaud, L.: Beiträge zur Kenntnis intrathyreoideal gelegener Zellhaufen der Parathyreoidea. Virchow's Arch. f. path. Anat. [etc.], Berl., 1908, **191**, 63-70.

Pfeiffer, H. & Mayer, O.: Experimentelle Beiträge zur Kenntnis der Epithelkörperchenfunktion. Mitt. a. d. Grenzeb. d. Med. u. Chir., Jena., 1908, **18**, 377-434.

*Thompson, R. L. & Harris, D. L.: A consideration of the pathological histology of the parathyroid glandules, and a report of a parathyroid-like tumor. J. M. Research., Bost., 1908, **19**, 135-152.

*Thompson, R. L. & Leighton, W. E.: The results of chronic parathyroiditis as obtained by ligation of the parathyroid glandules in the dog. J. M. Research, Bost., 1908, **19**, 121-133.

Yanase, J.: Ueber Epithelkörperbefunde bie galvanisher Uebererregbarkeit der Kinder. Jahrb. f. Kinderh., Leip. 219, 1908, **67**, 57-122.

1909

Bérard, L. & Alamartine, H.: Les parathyroides externes de l' homme. Compt. rend. Soc. de biol., Par., 1909, **66**, 619-621.

*Dock, G.: The parathyroid glands. In Osler's Modern Med., Phila., 1909, Lea & Febiger, **6**, 382-390.

*Escherich, T.: Die Tetanie der Kinder. Wien. Hölder, 1909.

Geis, N. P.: Thyroid lesions and the relations of the parathyroids in thyroid surgery. Med. Brief, St. Louis, 1909, **37**, 445-447.

*MacCallum, W. G. & Voegtlin, C.: On the relation of tetany to the parathyroid glands and to calcium metabolism. J. Exper. M., N. Y., 1909, **11**, 118-151.

McCarrison, R.: Observations on endemic cretinism in the Chitral and Galgit Valleys. Proc. Roy. Soc. Med., Lond., 1909, **2**, 1-36.

*Mayo, C. H.: The parathyroid question. Med. Sect., N. Y. M. J., N. Y., 1909, **90**, 184-185.

Parhon, C. & Goldstein: Influence de l'allaitement maternel sur la suivie des petits animaux thyroparathyroidectomisés. Compt. rend. Soc. de biol., Par., 1909, **66**, 330-332.

Pepere, A.: Della presenze di ghiandole salivari nel sistema tiro-paratiroideotimico dell 'uomo. Arch. ital. di anat. e di embriol., Firenze, 1909, **8**, 408-424.

Znojemsky, J.: Experimentalstudie über die Funktion der Schilddrüse und der parathyreoidealen Epithelkörperchen. Rev. de méd. tchèque, Prag., 1909, **2**, 48-50.

1910

Alessandri, R.: Adenoma della tiroide d'origine paratiroidea. Bull. d. r. Acad. med. di Roma, 1910, **36**, 64-68.

*Aschenheim, E.: Ueber den Aschegehalt in den Gehirnen Spasmophiler. Monatschr f. Kindehr., Leipz. & Wien., 1910, **9**, 366-375.
Bircher, E.: Die Organotherapie der postoperativen parathyreopriven Tetanie. Med. klin., Berl., 1910, **6**, 1741-1743.
*Carlson, A. J. & Jacobson, Clara: The depression of the ammonia-destroying power of the liver after complete thyroidectomy. Am. J. Physiol., Bost., 1910, **25**, 403-418.
Danielsen, W.: Erfolgreiche Epithelkörperchentransplantation bei Tetania parathyreopriva. Betir. z. klin. Chir., Tübing. 1910, **66**, 85-100.
Delore, X. & Alamartine, H.: La tétanie parathyréopriva postopératoire, et la technique des thyroidectomies, principalement dans la maladie de Basedow (technique de la thyroidectomie sous—capsulaire postérieure). Rev. d. Chir., Par., 1910, **30**, 540-576.
Edmunds, W.: Further observations on the thyroid (VII). J. Path. & Bacteriol., Cambridge, 1910, **14**, 288-293.
Ochsner, A. J. & Thompson, R. L.: The surgery and pathology of the thyroid and parathyroid glands. St. Louis, 1910, C. V. Mosby Co., 391 p.
Piradoff, R. B.: [Tetania et psychosis strumipriva.] Trudi i Protok. Imp. Kavkazsk., Med. Obsh., 1910-11, **47**, 298-301.
*Schabad, I. A.: Metabolism of calcium in children's tetany. Monatschr. f. Kinderh., 1910-11, Leipz. & Wien., **9**, 25-35.
Schäfer, E. A.: The thyroid and parathyroid glands throughout vertebrates, with observations on some other closely related structures. Phil. Tr. Lond., 1910, S. B. **201**, 91-132; 1911, S. B., **201**, 91-132.
*Schlesinger, H.: Ueber ein bisher unbekanntes Symptom bei Tetanie (Beinphanömen). Wien. klin. Wchnschr., 1910, **23**, 315-317.

1911

Arteaga, J. F.: Las glandulas paratiroideas, apuntes de fisiologia. Rev. méd. cubana, 1911, **19**, 335-338.
*Bliss, R. W.: A study of the parathyroid glands, with especial reference to infantile tetany. Arch. Pediat., N. Y., 1911, **28**, 892-904.
Bobeau, G.: Recherches cytologiques sur les glandules parathyroides du cheval. Paris, 1911, Alcan, 43 p.
*Carlson, A. J. & Jacobson, Clara: Further studies on the nature of parathyroid tetany. Am. J. Physiol., Bost., 1911, **28**, 133-160.
Edmunds, W.: Further observations on the thyroid gland (VIII). J. Path. & Bacteriol., Cambridge, 1911-12, **16**, 481-484.
Fischer, E.: Die glandulae parathyreoideae des Menschen. Arch. f. Anat. u. Entwcklngsgesch., Leipzig, 1911, 133-162.
Giuzzetti, P.: Sul glucogeno delle paratiroidi. Atti d. Cong. internaz. dei patol., 1911-12, **1**, 219-224.
*Greenwald, I.: The effect of parathyroidectomy upon metabolism. Am. J. Physiol., Bost., 1911, **28**, 103-132.
Grosser, P.: Epithelkörperchen-Untersuchungen bei Kindern. Verhandl. d. Versammi. d. Gesellsch. f. Kinderh.....Deutsch. Naturf. u. Aertze, 1911, **28**, 140-149.
Guleke: Experimentelle Untersuchungen über Tetanie. Arch. f. klin. Chir., Tübing., 1911, **94**, 496-532.
Iversen, T.: Studier over Glandulae parathyreoidea, saerlig deres Forhold til Struma og Morbus Basedowii. Kjobenhavn, 1911, 344 p.
Jovane, A. & Vaglio, R.: Tetania e paratirodi. Atti. d. Cong. pediat. ital., 1911, **7**, 478-482.
Krabbel, M.: Zur Behandlung der Tetania parathyreopriva mit Ueberpflanzung von Epithelkörperchen, Tübingen, 1911, Laupp, 27 p.
Leischner, H. & Köhler, R.: Ueber homoplastische Epithelkörperchen und Schilddrüsenverpflanzung. Arch. f. klin. Chir., Tübing., 1911, **94**, 169-185.
*MacCallum, W. G.: The seat of action in tetany after parathyroidectomy. Proc. Soc. Exper. Biol. & Med., N. Y., 1911, **9**, 23-24.
*Mayo, C. H. & McGrath, B. F.: Parathyroids and their surgical relation to goitre. South. Surg. & Gynec. Tr., 1911, **24**, 151-160.
*Mustard, H. J.: A study of certain tonic and reflex nervous impulses as factors in a parathyroid tetany. Am. J. Physiol., Bost., 1911-12, **29**, 311-316.
Schafermann, Rose: Études sur les lapins parathyroidectomisés. Lausanne, 1911, Imprim. de l'Univ., 24 p.
*Simpson, S.: The influence of age on the symptoms following thyroparathyroidectomy. Proc. Soc. Exper. Biol. & Med., N. Y., 1911-12, **9**, 2-4.

Steblin-Kaminski, G. Ye.: [Two cases of parathyroid goitre.] Khirug. Arkh. Velyaminova, 1911, **27,** 685.
Stuckenberg, Sophie: Ueber einen Fall von chronischer Tetanie mit Epithelkörperchenbefund, Berl., 1911, Ebering, 30 p.
Thompson, F. D.: The thyroid and parathyroid glands throughout vertebrates, with observations on some other closely related structures. Tr. Roy. Soc., Lond., 1911, **201,** 91-132.
*Wilcox, H. B.: The relation of parathyroid glands to electrical hyperirritability. Proc. Soc. Exper. Biol. & Med., N. Y., 1911-12, **9,** 67-70.
Wrede: Tetanie nach Strumaoperation. Kor-Bl. d. allg. ärztl. Ver. v. Thürigen, 1911, **40,** 518.

1912

*Carlson, A. J.: Parathyroid tetany and active immunity. Proc. Soc. Exper. Biol. & Med., N. Y., 1912-13, **10,** 187-188.
The parathyroids and pregnancy. Proc. Soc. Exper. Biol. & Med., 1912-13, **10,** 183-188.
The condition of the digestive tract in parathyroid tetany in cats and dogs. Am. J. Physiol., Bost., 1912-13, **30,** 309-340.
Frouin, A.: Reproduction chez les chiennes thyroparathyroidées (note preliminaire). Compt. rend. Soc. de biol., Par., 1912, **72,** 249.
Ginsburg, N.: The surgical anatomy of the parathyroid glands and allied lmpth nodes. Tr. Phila. Acad. Surg., 1912, **14,** 26.
The surgical importance of the parathyroid glands and closely allied lymph-nodes. J. Am. M. Ass., Chicago, 1912, **58,** 1668-1671.
Gjestland, G.: Ein Fall von Paralysis agitans mit bedeutender Vergrösserung der Glandulae parathyreoideae. Ztschr. f. klin. Med., Berl., 1912, **76,** 237-241.
Grulee, C. G.: The relation of the parathyroid glands to infant tetany. J. Am. M. Ass., 1912, **59,** 938.
Gussio, S.: Contributo alla casistica e sintomatologia dei tumori paratiroidei. Ann. d. r. Ist. di clin. chir. di Roma, 1912, **4,** 73-103.
*Halsted, W. S.: Report of a dog maintained in good health by a parathyroid autograft approximately one-fourth of a millimeter in diameter, and comments upon the development of the operation for Graves' disease as influenced by the results of experiments on animals. J. Exper. M., N. Y., 1912, **15,** 205-215.
*Hohlbaum, J.: Beiträge zur Kenntnis der Epithelkörperchenfunktionen. Betir. z. path. Anat. u. z. allg. Path., Jena, 1912, **53,** 91-104.
*Iversen, T.: Das Verhältnis der glandulae parathyroideae bei Struma und Morbus Basedowii. Arch. internat. de chir., 1912-13, **6,** 154-221; 255-342.
*Jacobson, Clara: The effects of blood transfusion in parathyroid tetany. Am. J. Physiol., Bost., 1912-13, **30,** 47-55.
*Koch, W. F.: On the occurrence of methyl guanidine in the urine of parathyroidectomized animals. J. Biol. Chem., Balt., 1912, **12,** 313-315.
Lathrop, W.: Tetany following thyroidectomy. N. Y. M. J., N. Y., 1912, **96,** 693-694.
Laignel-Lavastine, L. & Duhem, P.: Les glandules parathyroides. Compt. rend. Soc. d. biol., Par., 1912, **72,** 82-84.
Legàle, M.: La reazione attuale del siero di sangue negli sparatiroidati. Pathologica, Geneva, 1912-13, **5,** 149.
*MacCallum, W. G.: The function of the parathyroid glands. J. Am. M. Ass., 1912, **59,** 319-322.
Meriggio, G.: La paratiroidina Vassale nella corea, nell' eclampsia puerperale a nell' uremia convulsiva da nefrite scarlatinosa. Biochim. e. terap. sper., Milano, 1912-13, **4,** 127-142.
Minea. L. & Radovici. A.: Sur l'influence de l'opothérapie parathyroidienne sur la régénérescence des nerfs sectionnés chez les animaux thyroparathyroidectomisés. Compt. rend. Soc. de biol., Par., 1912, **72,** 840-842.
Mollgaard. H.: Ueber Veränderungen im Zentralnervensystem bei der Tetania parathyreopriva. Skandin. Arch. f. Physiol., Leipz., 1912, **28,** 65-90.
Morel, L.: Les parathyroides et la fonction maternelle. Gynécol., Par., 1912, **16,** 193-205.
L'insuffisance parathyroidienne et son traitement. Paris med., 1912-13, **9,** 361-366.
La greffe parathyroidienne. Arch. gén. de chir., Par., 1912, **6,** 512-538.
*Morel, L. & Rathery, F.: Le foie du chien parathyroprivé. J. de Physiol. et de path. gén., Par., 1912, **14,** 901-906.
*Pool, E. H. & Turnure, P. R.: Post-operative tetany: parathyroid transplantation. Ann. Surg., Phila., 1912, **56,** 804-807.

*Proescher, F. & Diller, T.: A fatal case of tetany with autopsy findings showing hemorrhages in the parthyroid glands. Am. J. M. Sc., Phila., 1912, **143,** 696-708.

*Rhinehart, D. A.: The nerves of thyroid and parathyroid bodies. Am. J. Anat., Phila., 1912, **13,** 91-102.

Roussy, G.: Les parathyroides; anatomie et physiologie normales et pathologiques. J. med. franc., Par., 1912, **6,** 111-121.

Salvioli, J. & Carraro, A.: Ueber die Wirkung der Parathyreoidextrakte. Verhandl. d. deutsch. path. Gesellsch., 1912, **15,** 264-266.

Shepherd, F. J.: Tetany following extirpation of the thyroid; with report of a case. Ann. Surg., Phila., 1912, **56,** 665-674.

Silvan, C.: Su di una speciale formazione epiteliale annesse al sistema tiro-paratiroideo. Bull. d. Soc. med. di Parma., 1912, 2.s., **5** 32-41.

Todyo, R.: Ueber das Verhalten der Epithelkörperchen bei Osteomalacie und Osteoporose. Frankfurt. Ztschr. f. Path., Wiesb., 1912, **10,** 219-241.

1913

Alquier, L. & Hallion, L.: Modifications histologiques du thyroide chez le lapin après ingestion d'extraits de parathyroide, d'hypophyse et de surrénale. Rev. neurol., Par., 1913, **26,** 41-43.

Avtokratoff, D. M.: [Anatomy and physiology of the thymus, thyroid and parathyroid glands, in connection with the question of their internal secretion.] Vestnik obsh. vet., 1913, **25,** 65-73.

Baggio, G.: Ricerche sperimentali introno all' influenza delle paratiroidi timiche sulla tetania paratireopriva del consiglio. Arch. per le sc. med., Torino, 1913, **37,** 354-366.

*Biedl, A.: Innere Sekretion. Wien., 1913, Urban & Schwarzenberg, v. **1,** 534 p.; v. **2,** 692 p.

*Boldyreff, W. N.: Der Einfluss des Schilddrüsenapparates auf die Wärmeregulierung bei Hunden. Die Methode der Hervorrufung und Heilung der krankhaften Anfälle, die bei Hunden nach Exstirpation der Schild—und Nebenschilddrüsen typisch sind. Arch. f. d. ges. Physiol., Bonn, 1913, **154,** 470-491.

*Carlson, A. J.: The tonus and hunger contractions of an empty stomach during parathyroid tetany. Am. J. Physiol., Balt., 1913, **32,** 398-404.

*Edmunds, W.: Further observations on the thyroid gland (IX). J. Path. & Bacteriol., Cambridge, 1913-14, **18,** 52-59.

Frias, M.: Contribution à l'étude des glandes parathyroides. Arq. do Inst. bacteriol., Camara Pestana, 1913, **4,** 75-91.

Greenwald, I.: Further metabolism experiments upon parathyroidectomized dogs. J. Biol. Chem., Balt., 1913, **14,** 363-367.

Guleke, N.: Chirurgie der Nebenschilddrüsen (Epithelkörper). Stuttgart, 1913, Enke, 216 p.

Halpenny, J.: The thyroid and parathyroid problem. Surg. Gynec. & Obst., Chicago, 1913, **16,** 595-600.

*Hertz, A. F.: A case of parathyroid insufficiency. Guy's Hosp. Rep., Lond., 1913, **52,** 3.s., 153-155.

Hornowski, J.: [Anatomic-pathological investigation on the relation of the thymus gland to the parathyroid glands and on its behavior in the lymphatic, thymic and thymico-lymphatic status]. Lwow. tygodn. lek., 1913, **8,** 577.

*Koch, W. F.: Toxic bases in the urine of parathyroidectomized dogs. J. Biol. Chem., Balt., 1913, **15,** 43-63.

Lombroso, U. & Artom, C.: Sull' importanza dell' apparato tireoparatiroideo nell' assimilazione degli idrati di carbonio. Arch. di farmacol., sper., 1913, **16,** 289-298.

*MacCallum, W. G.: Die Nebenschilddrüsen. Ergebn. d. inn. Med. u. Kinderh, Berl., 1913, **11,** 569-610.

*MacCallum, W. G. & Vogel, K. M.: Further experimental studies in tetany. J. Exper. M., Lancaster, Pa., 1913, **18,** 618-650.

*MacCallum, W. G.: The parathyroids, Louisville Month. J. M. & S., 1913-14, **20,** 313.

*Marine, D.: Parathyroid hypertrophy and hyperplasia in fowls. Proc. Soc. Exper. Biol. & Med., N. Y., 1913-14, **11,** 117-118.

*Massaglia, A.: Tetanie infolge experimenteller Parathyreoidinsuffizenz während der Schwangerschaft und Eklampsie. Centralbl. f. allg. Path. u. path. Anat., Jena, 1913, **24,** 577-581.

Maurer: Schilddrüse, Thymus und ihre Nebendrüsen bei Wirbeltieren und dem Menschen. München. med. Wchnschr., 1913, **60,** 724-726.

*McCarrison, R.: Experimental researches on the etiology of endemic cretinism, congenital goitre and congenital parathyroid disease. Indian J. Med. Res., Calcutta, 1913, **1**, 505-522.

McLean, F. C.: Ueber den Kohlehydratumsatz des isolierten Herzens thyreo—und parathyreopriver Kaninchen. Zentralbl. f. Physiol., 1913, **27**, 582.

McNabb, C. P.: The influence on metabolism of the thyroid and parathyroid glands. Charlotte M. J., 1913, **68**, 154-156.

Morel, L.: Les relations fonctionnelles entre le foie et les parathyroides. Compt. rend. Soc. de biol., Par., 1913, **74**, 28-30.
Les parathyroides. Biologica, 1913, **3**, 1-8.

*Pavloff: [Exchange of gases and metabolism on different diets after removal of the parathyroid glands.] Ann. d. k. Univ. Kharkov., 1913, **1**, 253.

1913

Pavloff, M.: Zur Frage der Funktion der Glandulae parathyreoideae. Lab. d. allg. Pathol. an d. Universitat Kharkow, 1913, Centralbl. f. allg. Path. u. path. Anat., Jena, 1114, **25**, 890.

Poggio, E.: Insufficienza paratiroidea cronica ed innesto di tiroide. Riv. crit. di clin. med., Firenze, 1913, **14**, 769-777.

Quarelli, G.: Tetania ed innesto tiroideo. Gior. d. r. Accad. di med. di Torino, 1913, 4.s., **19**, 169-179.

Segàle, M.: Réaction actuelle du sérum de sang chez les individus parathyreoidectomisés. Arch. Ital. de biol., Torino, 1913, **60**, 191-194.

*Simpson, S.: Age as a factor in the effects which follow thyroidectomy and thyro-parathyroidectomy in the sheep. Quart. J. Exper. Physiol., Lond., 1913, **6**, 119-145.

*Werelius, A.: Do the parathyroids functionate in intrauterine life? Surg. Gynec. & Obst., Chicago, 1913, **16**, 141-144.

1914

Bergeim, O., Stewart, F. T. & Hawk, P. B.: Calcium metabolism after thyro-parathyroidectomy. J. Exper. M., Lancaster, Pa., 1914, **20**, 226-236.

Churchill, C. H.: A study of the parathyroid glands. J. Iowa State M. Soc., Clinton, 1914, **4**, 151-158.

Harrower, H. R.: The properties of parathyroid extracts. N. Y. M. J., N. Y., 1914, **99**, 420-424.

*Hoskins, R. G. & Wheelon, H.: Parathyroid deficiency and sympathetic irritability. Am. Jour. Physiol., Balt., 1914, **34**, 236-270.

*Hunter, A.: The influence of early removal of the thyroid and parathyroid glands upon nitrogenous metabolism in the sheep. Quart. J. Exper. Physiol., Lond., 1915, **8**, 23-32.

*Keeton, R. W.: The secretion of the gastric juice during parathyroid tetany. Am. J. Physiol., Balt., 1914, **33**, 25-49.

*MacCallum, W. G.: The parathyroid gland; a brief digest of the literature of 1912-13, Am. Med., Burlington, Vt., 1914, n.s., **9**, 244-248.
The parathyroids. Post Grad., 1914, **20**, 91.

*MacCallum, W. G., Lambert, R. A. & Vogel, K. M.: The removal of calcium from the blood by dialysis in the study of tetany. J. Exper. M., Lancaster, Pa., 1914, **20**, 149-168.

*Marine, D.: Observations on tetany in dogs; relation of the parathyroids to the thyroid; relation of tetany to age, amount of parathyroid tissue removed, accessory parathyroids, pregnancy, lactation, rickets, sulphur and diet; relation of parathyroids to sugar tolerance; effect of calcium salts. J. Exper. M., Lancaster, Pa., 1914, **19**, 89-105.

*McCarrison, R.: Etiology of endemic cretinism, congenital goitre, and congenital parathyroid disease; abstract of experimental researches. Lancet, Lond., 1914, **1**, 817-819.

Pepere, A.: Per una più esatta interpretazione patogenetica della tetania infantile d'origine paratiroidea. Riforma med., Napoli, 1914, **30**, 1375-1380.
Su la esistenza di un tessuto paratiroideo transitorio fetale nell' uomo. Arch. f. Entwcklngsmechn. d. Organ., Berl., 1914, **40**, 253-278.

Shumkova-Trubina, Klavdiya Grigoryevna: [Transplantation of the thyroid and parathyroid glands into different organs and tissues. Experimental investigation.] Kazan, 1914, 129 p.

*Simpson, S. & Rasmussen, A. T.: The effect of thyro-parathyroidectomy on the blood coagulation time in the dog. Proc. Soc. Exper. Biol & Med., N. Y., 1914-15, **12,** 96-98.

Singer, G.: Das thyreo-parathyreo-thymische System und das Abderhaldensche Dialysieryerfahren, Ztschr. f. Kinderh., 1914, **10,** 71-80.

*Stoland, O. O.: The influence of parathyroid tetany on the liver and the pancreas. Am. J. Physiol., Balt., 1914, **33,** 283-299.

Tanberg, A.: Acute and chronic tetany after parathyroidectomy, Tideskr. f. d. norske Laegefor., Kristiania, 1914, **34,** 969-978.
Ueber die chronische Tetanie nach Exstirpation von Gl. parathyreoideae. Mitt. a. d. Grenzgeb, d. Med. u. Chir., Jena, 1914, **27,** 575-605.

Thimm, L.: Zur Kenntnis der Epithelkörperchen (Glandulae parathyreoideae). Arch. f. Kinderh., Leipz., 1914 **63,** 321-344.

*Underhill, F. P., & Blatherwick, N. R.: Studies in carbohydrate metabolism VI. The influence of thyreoparathyroidectomy upon the sugar content of the blood and the glycogen content of the liver. J. Biol. Chem., Balt., 1914, **18,** 87-90.

*Urechia, C. I.: L'urée dans le sang et dans l'urine des chiens thyroparathyroidectomisés, Arch. de méd. exper. et d'anat. path., Par., 1914-15, **26,** 86-93.

1915

*Dock, G.: The parathyroid glands, In: Osler, William & McCrae, Thomas, Modern Medicine, Philadelphia, 1915, Lea & Febiger, **v. 4,** 898-904.

*v. Eiselsberg, E.: Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen und Nebenschilddrüsen, zugleich ein Beitrag zur postoperative Tetania parathyreopriva. Arch. f. klin. Chir., 1915, **106,** 1-15.

*Falta, W.: The ductless glandular diseases. (Trans. by Meyers, M. K.), Phila., 1915, P. Blakiston's Son & Co., **602,** p. 8°.

Fulci, F., & Giannuzzi, A.: Ueber die Regenerationsfähigkeit der Parathyreoidea. Centralbl. f. allg. Path. u. path. Anat., Jena, 1915, **26,** 97-99.

*Gley, E.: The theory of internal secretion: Its history and development. Practitioner, Lond., 1915, **94,** 2-15.

Hanes, E. L.: The parathyroids and tetany. N. Y. Med. J., N. Y., 1915, **101,** 1327-1329.

*Harbitz, F.: On tumors of the parathyroid glands. J. M. Research, Bost., 1915, **32,** 361-375.

*Hertz, A. F.: The parathyroid glands. Practitioner, Lond., 1915, **94,** 107-111.

Hewitson, W. A.: The significance of the thyro-parathyroid mechanism, with special reference to its metabolic functions. Univ. Durham Coll. Med. Gaz., 1915-16, **14,** 45-51.

Johnston, G. B., & Budd, S. W.: Tetany following parathyroidectomy, with report of a case following partial thyroidectomy. South. M. J., Nashville, 1915, **8,** 135-143.

*Koch, W. F.: The physiology of the parathyroid glands. J. Lab. & Clin. M., St. Louis, 1915-16, **1,** 299-315.

*Morris, R. S.: On the probable toxic effects of prolonged administration of the parathyroid gland. J. Lab. & Clin. M., St. Louis, 1915-16, **1,** 26-30.
On the probable toxic effects of prolonged administration of parathyroid gland. Tr. Assn. Am. Phys., Phila., 1915, **30,** 620-626.

*Paton, D. N., Findlay, L., & Burns, D.: On guanidin or methylguanidin as a toxic agent in the tetany following parathyroidectomy. J. Physiol., Lond., 1914-15, **49,** xvii-xviii.

*Pool, E. H.: The parathyroid glands. Internat. Abstr., Chicago, 1915, **20,** 465-478.

Rossiisky, D. M.: [Case of tetany successfully treated with parathyroid extract.] Russk. Vrach., Petrograd, 1915, **14,** 877-880.

Schlagenhaufer: Zwei Fälle von Parathyreoideatumoren. Wein. klin. Wchnschr., 1915, **28,** 1362.

*Wilson, D. W., Stearns, T., & Janney, J. H., Jr.: The effect of acid administration on parathyroid tetany. J. Biol. Chem., Balt., 1915, **21,** 169-177.

*Wilson, D. W., Stearns, T., & Thurlow, Madge DeG.: The acid-base equilibria in the blood after parathyroidectomy. J. Biol. Chem., Balt., 1915, **23,** 89-121.

*Wilson, D. W., Stearns, T., & Janney, J. H., Jr.: The excretion of acids and ammonia after parathyroidectomy. J. Biol. Chem., Balt., 1915, **23**, 123-138.

1916

Burns, D., & Sharpe, J. S.: The parathyroids: tetania parathyreopriva; its nature, cause, and relations to idiopathic tetany. Part V. Guanidin and methyl-guanidin in the blood and urine in tetania parathyreopriva and in the urine in idiopathic tetany. Quart. J. Exper. Physiol., Lond., 1916, **10**, 345-354.
Part VII. A comparison of the influence on the protein metabolism of parathyroidectomy and of the administration of guanidin. Quart. J. Exper. Physiol., Lond., 1916, **10**, 361-376 .

Coleman, R. B.: Tetany after thyroidectomy, recovery. Brit. M. J., Lond., 1916, **ii**, 871.

Edmunds, W.: Further observations on the thyroid gland (X). J. Path. & Bacteriol., Cambridge, 1916-17, **21**, 23-27.

*Greenwald, I.: Some observations on the tetany of parathyroidectomized dogs. J. Biol. Chem., Balt., 1916, **25**, 223-226.

*Holmes, J. B.: The reliability of the electrical diagnosis of tetany, with especial consideration of the electrical value found in normal children. Am. J. Dis. Child., Chicago, 1916, **12**, 1-29.

*Howland, J., Haessler, F. H., Marriott, W. McK.: The use of a new reagent for microcolorimetric analysis as applied to the determination of calcium and of inorganic phosphates in the blood serum. J. Biol. Chem., Balt., 1916, **24**, xviii-xix.

*Jackson, C. M.: Effects of inanition upon the structure of the thyroid and parathyroid glands of the albino rat. Am. J. Anat., Phila., 1916, **19**, 305-352.
Effects of inanition upon the structure of the thyroid and parathyroid glands of the albino rat. Anat. Record, Phila., 1915-16, **10**, 208-209.

Kendall, E. C.: The function of the thyroid-parathyroidapparatus. J. Am. M. Ass., Chicago, 1916, **66**, 811-813.

Laureati, F.: Sindrome da insufficienza tireo-paratiroidea familiare. Pediatria, Napoli, 1916, 2 s., **24**, 411-418.

Massaglia, A.: Tetania da insufficienza paratiroidea sperimentale nella gravidanza ed eclampsia. Gazz. d. osp., Milano, 1916, **37**, 580-582.

*Paton, D. N., & Findlay, L.: Part IV. The etiology of the condition and its relationship to guanidin and methyl-guanidin intoxication. Quart. J. Exper. Physiol., Lond., 1916, **10**, 315-344.
Part VIII. The functions of the parathyroids and the relationship of tetania parathyreopriva to idiopathic tetany. Quart. J. Exper. Physiol., Lond., 1916, **10**, 377-382.

*Paton, D. N., & Findlay, L.: The parathyroids: tetania parathyreopriva; its nature, cause and relations to idiopathic tetany. Part I. Introduction general methods and symptoms. Quart. J. Exper. Physiol., Lond., 1916, **10**, 203-231.

*Paton, D. N., Findlay, L., & Watson, A.: Part II. The parts of the central nervous system involved. Quart. J., Exper. Physiol., Lond., 1916, **10**, 233-242.
Part III. The changes in the peripheral nerves and in the muscles. Quart. J. Exper. Physiol., Lond, 1916, **10**, 243-314. Part IV. The etiology of the condition and its relationship to guanidin and methyl-guanidin intoxication. Quart J. Exper. Physiol., Lond., 1916, **10**, 315-344.

*Peterson, W., Jobling, J. W., & Eggstein, A. A.: Serum changes following thyroparathyroidectomy; studies on ferment action. XXXI. J. Exper. M., 1916, Balt., **23**, 499-505.

Petit, G.: Cancer thyroidien aberrant chez le cheval. Rec. de méd. vét., Par., 1916, **92**, 326-331.

*Pool, E. H., & Falk, H. C.: Concerning the surgical anatomy of the thyroid with special reference to the parathyroid glands. Ann. Surg., Phila., 1916, **63**, 71-77.

*Schlagenhaufer: Zwei Fälle von Parathyreoideatumoren. München. med. Wchnschr., 1916, **63**, 56.

Servetti, Larraya, J.: Reumatismo cronico tiroideo. Rev. méd. d. Uruguay, Montevideo, 1916, **19**, 829-842.

Shurley, B. R.: Thyroid disease in relation to rhinology and laryngology. J. Am. M. Ass., Chicago, 1916, **67**, 1726-1729.

*Simpson, S., & Rasmussen, A. T.: Does thyroparathyroidectomy in the dog affect the blood coagulation time? Quart. J. Exper. Physiol., Lond., 1916-17, **10,** 145-157.

*Tanberg, A.: The relation between the thyroid and parathyroid glands. J. Exper. M., Balt., 1916, **24,** 547-559.

Vermeulen, H. A.: Over glandulae parathyroideae (epitheelli-chaampjes). Nederl. Tijdschr.. v. Geneesk., Amst., 1916, **(II),** 1779-1789.

*Wishart, G. M.: The parathyroids: tetania parathyreopriva: its nature, cause, and relations to idiopathic tetany. Part VI. The action of the blood serum of animals in tetania parathyreopriva on the skeletal muscles of the frog. Quart. J. Exper. Physiol., Lond,. 1916, **10,** 355-360.

*Wood, F. C.: Thyroid and parathyroid tumors of the tongue. Proc. N. York Path. Soc., 1916, **16,** 84-89.

1917

Asher: Eine Untersuchung ob während des parathyreopriven Anfalles im Organismus giftige Stoffe kreisen? Cor.- Bl. f. schweiz. Aertze, Basil, 1917, **47,** 301.

*Binger, C.: Toxicity of phosphates, in relation to blood calcium and tetany. J. Pharm. & Exper. Therap., Balt., 1917, **10,** 105-120.

Bjure, A.: Bidrag till parathyroideakortlarnos aldersanatomi hos kanmen. Upsala läkaref. förh., 1917-18, n.f., **23,** 175-228.

Forsyth, D.: Tetany and the functions of the parathyroids. Brit. M. J., Lond., 1917, **i,** 632.

Herlihy, J. D.: Notes on a case of tetania parathyreopriva complicating pregnancy. Med. J. Australia, Melbourne, 1917, **ii,** 204.

*Kojima, M.: Studies on the endocrine glands: Paper I. The relations between the pancreas and thyroid and parathyroid glands. Quart. J. Exper. Physiol., Lond., 1917, **11,** 255-318.
Studies on the endocrine glands. II. The relations of pituitary blood with the thyroid and parathyroid and certain other endocrine organs in the rat. Quart. J. Exper. Physiol., Lond., 1917, **11,** 319-338.
Studies on the endocrine glands: III. The effects on the thyroid and parathyroid of the rat of administering thyroid extract and certain other autacoids and salts. Quart. J. Exper. Physiol., Lond., 1917, **11,** 339-345.
Studies on the endocrine glands. IV. The effects in the dog upon the remainder of the thyroid and parathyroid of partial removal of those organs. Quart. J. Exper. Physiol., Lond., 1917, **11,** 347-349.
Studies on the endocrine glands. V. Effects upon metabolism of castration, of thyroidectomy, of parathyroidectomy, and thyroid and parathyroid feeding. Quart. J. Exper. Physiol., Lond., 1917, **11,** 351-380.

Laméris, H. J.: Tetania parathyreopriva. Nederl. Tijdschr. v. Geneesk., Amst., 1917, **(I),** 856-860.

1917

*Marriott, W. McK.: & Haessler, F. H.: A micro method for the determination of inorganic phosphates in the blood serum. J. Biol. Chem., Balt., 1917, **32,** 241-243.

*Marriott, W. McK., & Howland, J.: A micro method for the determination of calcium and magnesium in blood serum. J. Biol. Chem., Balt., 1917, **32,** 233-239.

Passow, A.: Wird die Lebensfähigkeit transplantierter Epithelkörper durch die Anwendung von Lokalanästhesie bei der Verpflanzung beeinträchtigt? Strassburg, 1917, 24 p.

*Paton, D. N., Findlay, L., Watson, A., Burns, D., Sharpe, J. S., & Wishart, M.: Tetany and the functions of the parathyroids. Brit. M. J., Lond., 1917, **i,** 575-577.

Pflüger: Demonstration: Eine 33 jährige Patientin, bei der nach Strumaoperation Tetanie und im deren beiderseitage Cataract aufgetreten ist. Cor.-Bl. f. schweiz. Aertze., Basil, 1917, **47,** 1238.

Pool, E. H.: The relation of the parathyroid system to the female genital apparatus. Tr. Am. Gynec. Soc., Phila., 1917, **42,** 79-102.

Rémond, A.: Du rôle de l'association thyroparathyroidienne dans l'urémie. Bull. de l'Acad. de med., Par., 1917, 3 s., **77,** 504-507.

Sandelin, T.: [The blood picture in a case of Basedow's disease, chlorosis and tetania parathyreopriva.] Finska läk.-sällsk. handl., Helsingfors, 1917, **59,** 90-103.

Stenvers, H. W.: [Influence of the parathyroid gland of horse on tetany parathyreopriva, controlled by creatin excretion in the urine.] Nederl. Tijdschr. v. Geneesk., Amst., 1917, **(1)**, 85-94.

Vermeulen, H. A.: Over glandulae parathyroideae (epitheellichaampjes). Tijdschr. v. Diergeneesk., 1917, **44**, 155-164.

*Voegtlin, C.: The physiological and pathological importance of the parathyroid gland from the experimental aspect. Surg., Gynec. & Obst., Chicago, 1917, **25**, 244-250.

Voegtlin, C.: The physiological and pathological importance of the parathyroid gland from the experimental aspect. Tr. Am. Gynec. Soc., Phila., 1917, **42**, 64-78.

Voegtlin, C.: The physiological and pathological importance of the parathyroid gland from the experimental aspect. Am. J. Obst., N. Y., 1917, **76**, 678-679.

White, M.: The thyroid and parathyroid glands. Chicago Med. Rec., 1917, **39**, 559-562.

Winkler, C.: [An observation clearly elucidating the influence of the parathyroid glands upon tetany strumipriva.] Nederl. Tijdschr. v. Geneesk., Amst., 1917, **(1)**, 768-770.

1918

Ball, C. F.: Vital thyroid-parathyroid activities. Vermont Med., Rutland, 1918, **3**, 17; 33.

Bjure, A.: The anatomy of the parathyroid glands of rabbits according to age. Upsala läkaref. förh., 1918, **23**, 175-228.

*Burns, D., & Watson, A. McL.: The effect of thyro-parathyroidectomy on the heart and circulation. I. Action on nervous control of the heart. J. Physiol., Lond., 1918, **52**, 88-94.

*Henderson, Pearl S.: The guanidin content of muscle in tetania parathyreopriva. J. Physiol., Lond., 1918, **52**, 1-5.

*Hertz, A. F.: A case of parathyroid insufficiency. Endocrinol., Los Angeles, 1918, **2**, 145-148.

*Howland, J., & Marriott, W. McK.: Observations upon the calcium content of the blood in infantile tetany and upon the effect of treatment by calcium. Quart. J. Med., Oxford, 1918, **11**, 289-319.

*Koch, W. F.: Tetany and the parathyroid glands. M. & S., 1918, **2**, 9-17.

*McCann, W. S.: A study of the carbon dioxide-combining power of the blood plasma in experimental tetany. J. Biol. Chem., Balt., 1918, **35**, 553-563.

Tomasczewski, Z.: Untersuchungen über das Verhalten der Glandulae parathyreoideae Menschen beim Vorhandensein von Kalkablagerungen im Organismus. Frankfuort. Ztschr. f. Path., Wiesb., 1918, **21**, 38-56.

*Uhlenhuth, E.: The antagonism between thyroid and parathyroid glands. J. Gen. Physiol., Balt., 1918, **1**, 23-32.

1919

Curschmann, Ueber sensible und sensorische Tetanie. München. med. Wchnschr., 1919, **66**, 983-985.

*Honeyman, T. J.: The thymus and tetany. J. Physiol., Lond., 1919, **53**, 207-210.

*Houssay, B. A.: The action of blood serum of the dog in a condition of tetania parathyreopriva on voluntary muscular tissue compared with that of normal serum. Quart. J. Exper. Physiol., Lond., 1919, **12**, 111-114.

*Löffler, W.: Ueber den Grundumsatz bei Störungen innersekretorischer Organe. Ztschr. f. klin. Med., Berl., 1919, **87**, 280-291.

Pulay, E.: [Effect of endocrine glands on therapy of skin disease; the thyroid and parathyroids.] Therap. Monastschr., Berl., 1919, **33**, 125.

*Uhlenhuth, E.: Further proof of the antagonism existing between the thymus and parathyroid. Proc. Soc. Exper. Biol. & Med., N. Y., 1919, **16**, 70-72.

*Wilson, D. W., Stearns, T., Janney, J. H., Jr., & Thurlow, Madge DeG.: Studies on parathyroid tetany. Johns Hopkins Hosp. Rep., Balt., 1919, **18**, 12-20.

*Woltman, H. W.: Tetany in the eunuchoid. Report of a case. J. Nerv. & Ment. Dis., N. Y., 1919, **50**, 433-448.

1920

*Allen, B. M.: The parathyroid glands of thyroidless Bufo larvae. J. Exper. Zool., Balt., 1920, **30**, 201-210.

Barach, A. L., & Murray, H. A.: Tetany in a case of sprue. J. Am. Ass., Chicago, 1920, **74**, 786-788.

*Brown, A., MacLachlan, Ida F., & Simpson, R.: The effect of intravenous injection of calcium in tetany and the influence of cod liver oil and phosphorus in the retention of calcium in the blood. Am. J. Dis. Child, Chicago, 1920, **19**, 414-428.

*Grant, S. B., & Goldman, A.: A study of forced respiration: Experimental production of tetany. Am. J. Physiol., Balt., **52**, 209-232.

*MacCallum, W. G., Lintz, J.: Vermilye, H. N., Leggett, T. H., & Boas, E.: The effect of pyloric obstruction in relation to gastric tetany. Johns Hopkins Hosp., Bull., Balt., 1920, **31**, 1-7.

McLean, S.: Seasonal incidence of tetany; a report of 47 cases. Arch. Pediat., N. Y., 1920, **37**, 85-88.

Parhon, M.: Sur la tepeur en glycogène du foie et des muscles chez les animaux thyroparathyroidectomisés. Compt. rend. Soc. d. biol., Par., 1920, **83**, 140-142.

*Vincent, S., & Arnason, J. S.: The relationship between thyroid and parathyroids. Endocrinol., Los Angeles, 1920, **4**, 199-204.

*Council on Pharmacy and Chemistry of the American Medical Association: Useful drugs, Chicago, 1920. Press Am. M. Ass.

EPILEPSY SUGGESTIVE OF ENDOCRINE RELATIONSHIP*

HENRY J. VAN DEN BERG, M. D., F. A. C. S.
GRAND RAPIDS, MICH.

The idea prevails with some of the laity that epilepsy is a surgical disease, and some members of the medical profession, possibly influenced by past literature, and at times discouraged with the rather slow results in its treatment, think possibly that surgery may offer more prompt relief. It is for this reason that every surgeon is approached by this class of patients. This is my excuse, if one is necessary, for presenting the subject before this society.

Epilepsy has long been divided into the symptomatic and idiopathic types. The symptomatic group comprises those in which a definite etiological basis is apparent, and included in this group are brain tumors and certain traumatic head conditions from which surgical relief is possible. The idiopathic group has been termed more appropriately "the epilepsies." Instead of "idiopathic," probably the word "unclassified," as suggested by Munson, would be more fitting. This unclassified group has at least a metabolic subdivision, and some workers think that the group in its entirety is dependent upon disturbed metabolism. In a large number of autopsies performed by Munson the number of cases in which pathological lesions were found was almost nil. Pathological physiology seems to offer the more promising field for eventually solving the problem.

The disease manifests itself through the nervous system, and it is generally believed that it is one resulting from diverse stimuli. Munson believes that its origin is in the central nervous system, and that a reaction of the nervous system may be produced either by a chemical change in the cell itself, or by the action of the stimuli reaching the nerve cells. The reaction produced in either case is similar. I do not believe that it has its origin in the central nervous system *per se*. It is more probable that it is the result of the action of external forces which tem-

* Read before the Detroit Surgical Society, February 11th, 1921.

porarily overcome the equilibrium of the nerve cells, though acting on cells that are possibly hypersensitive to such stimuli.

The trend of recent epileptologic research has been directed in large part to the gastro-intestinal tract and the glands of internal secretion. With regard to the gastro-intestinal tract, some American surgeons have done an enormous amount of work to show that the intestinal stasis in epileptics has been due to peritoneal bands, kinks and adhesions. By the surgical correction of these conditions they have attempted to cure or secure amelioration of the disease, with results which are quite doubtful. Caro, a worker in the Munson Hospital of Massachusetts, has shown from the study of a large number of autopsies, that intestinal kinks, adhesions and peritoneal bands are no more frequent in epileptics than non-epileptics. This finding is rather important from the standpoint of surgical attack of the disease, and it seems that we shall have to look elsewhere for means of combating the cause of epilepsy. Of course, we all know that constipation is the constant complaint of the epileptic, and the recent literature shows quite plainly that the dominant factor in the pathogenesis of the convulsions is impairment of metabolism, and that the spasmogenic agent is in the blood stream. This condition may well be brought about by intestinal stastis, but it seems to have been strictly proven that the causes of intestinal stasis in the epileptic do not differ at all from the causes in the non-epileptic. Bisgard and Novig have recently adduced some experimental evidence of disturbed metabolism, in that they regularly found an increased ammonia content in the blood of epileptics before an attack or its "psychic equivalent." Low values were obtained after the attack.

As the endocrine glands preside over our metabolic processes, and as epilepsy may be due to an impairment of metabolism, may they not, in many cases, play an important role in its production? With reference to this possibility, I wish to present eleven case histories as evidence pointing to the endocrine system taking a prominent part in some cases of this disease. It is interesting to note that these were consecutive cases. All were true epilepsies. In the histories I shall give only such data as may have bearing on the subject.

GROUP I. ONSET AT PUBERTY; SEIZURES AT TIME OF PERIODS.

Case 1—(Free during pregnancy). Female, married, age 27. The menstrual history is negative except that she flows scantily. Menstruation began at fifteen. Seizures commenced soon after the first menstrual period. She has had a seizure just prior to nearly every period since. The only period she has been free from seizures for any length of time was during her first pregnancy and for six months following; and during her second pregnancy, and for fourteen months following.

Case 2—Female, single, age 39, of nervous temperament. She had a few attacks of convulsions during childhood following an illness that was diagnosed as meningitis. She had whooping cough at three years of age. From her fourteenth year (puberty) until her nineteenth year she had a few petit mal attacks. Since then she has had grand mal seizures, which have been milder and less frequent the past year. They occur just prior to or just after menstruation.

Case 3—(Free after marriage). Female, single, age 23. Menstruation was established at thirteen; it is regular, but always scanty. At eight years of age she had an indefinite seizure. (She does not know about whooping cough.) No other attack was experienced until she was fifteen, which attack just preceded the first menstrual period. Since then she has had an attack with nearly every period, usually just before, but a few midway between periods. This patient was married two years ago and has not had an attack since.

Case 4—Female, single, age 38, of nervous temperament. Her flow is scanty. Menstruation began at seventeen. She has had seizures since she was eighteen. A few attacks have been experienced between periods, but eight of ten occur at menstrual time, usually just before the onset of flow.

Case 5—Female, single, age 26, of nervous temperament. Menstruation began at fifteen. Her first seizure was experienced soon after the first menstrual period. Seizures come at two to six months' intervals, always associated with the periods, and usually on the last day.

GROUP II. ONSET AT PUBERTY—TIME OF SEIZURES NOT KNOWN.

Case 6—(Termination at menopause). Married woman, age 64. Had epileptic seizures from her fifteenth to her fortieth year. Menstruation began at fifteen and the menopause appeared at forty. Seizures occurred only during the years of activity of the sex glands.

Case 7—Female, married, age 28. She has had two children. Her first seizure occurred at fifteen. Menstruation began at fifteen. Her second seizure occurred during the second pregnancy. Third and fourth attacks have recently been experienced. The records do not state the relation of the attacks to menstruation.

GROUP III. ONSET DURING PREGNANCY.

Case 8—Female, married, age 27, of nervous temperament. Her menstrual history was normal. She has one child four years old. At the time of the first seizure the patient was four and one-half months pregnant. The second occurred six weeks later, and the third four and one-half months after delivery. She nursed the baby. Since then she has had several attacks a year, and always about the time of the periods, usually just before.

Case 9—Female, married, age 34, of nervous temperament. Epileptic seizures began four years ago when she was seven months pregnant. She had one or two more during this pregnancy. Ten months after a normal labor another seizure was experienced. She has had

them ever since, usually a week after the period, on an average of one every second month. She nursed the baby and was still nursing it at the time of the first post-natal seizure.

GROUP IV. ONSET AFTER PUBERTY—SEIZURES AT TIME OF PERIODS.

Case 10—(Free during pregnancy.) Female, age 50, of nervous temperament, widow for nine years. Convulsions occurred from the first to the ninth year. At the age of nine menstruation was established, and the seizures stopped. She had whooping cough, but does not know at what age. Seizures began at eighteen. She was married at twenty and has had two children. She was free from seizures during pregnancy, and for several months afterward. Nine out of ten attacks come on the first day of the periods at intervals of one to a few months. During the past decade attacks have been more frequent. Immediately after marriage and before pregnancy the patient increased considerably in weight.

GROUP V. MALE CASE—ONSET ABOUT THE TIME OF PUBERTY.

Case 11—Male, age 17. The first attack was experienced at fifteen. He has had several seizures at varying intervals since.

In summing up these cases we find that the seizures began about the time of the establishment of menstruation in seven out of ten female cases. Of the remaining three cases, two began during pregnancy. In seven of the ten female cases the seizures occurred quite consistently about the menstrual time, usually just before. In two, the relation is not noted in the records, and in one, the attacks occurred one week after the periods. In two cases (1 and 10) the patients were free from attacks only during pregnancy and for some time following. Five had scanty menstruation. Case 3, in which the attacks ceased with the event of marriage, might suggest the possibility of a better endocrine balance, as the result of living a normal sexual life. In this class might be placed the point mentioned in Case 10, namely, considerable increase in weight after marriage and before pregnancy. I have seen other cases in which the increase in weight could not be attributed to better living habits, the sexual factor only being different. Case 6, with seizures beginning at puberty and ending at the menopause, is most interesting and suggests very strongly the metabolic influence. I know of another similar case, but it has not come under my personal observation.

In Cases 5 and 8 the patients had convulsions during childhood, and in Case 9 there was an indefinite seizure. Of these patients 5 and 8 had whooping cough during childhood, and in Case 9 this point is not known. This is very interesting in connection with the recent study of this relationship by Morse, who reports that convulsions in childhood are not likely to

eventuate in epilepsy, with the possible exception of those beginning with whooping cough.

It would seem that these points suggest strongly a connection between the disease and puberty, menstruation and pregnancy. In other words, in the majority of these cases the onset and the attacks occurred at a time when there was some radical change (puberty), adjustment or disturbance (menstruation and pregnancy), going on in the chemical laboratory of the body. With regard to the time of puberty, we all realize that this is the time of great activity of the endocrine system, as evidenced by the development of secondary sex characteristics. Also about this time we see quite frequently an enlargement of the thyroid gland in the so-called adolescent goitre. Dana states that the epileptic age is from ten to twenty, and still more definitely, from ten to fifteen. The period then of greatest endocrine activity corresponds to the period in which we see the greatest number of epileptics develop. In three-fourths of all Dana's cases the seizures began before the age of twenty.

During pregnancy as Erdheim has shown, there are definite histological changes in the hypophysis and this organ enlarges with each succeeding pregnancy. This change coincides with the clinical signs seen during pregnancy, which resemble acromegaly, manifesting themselves with such alterations as thickening of the lips or enlargement of the hands and feet. These changes are not permanent but only passing, and, therefore, might be regarded as amounting to acute acromegaly. Also, it is often stated that we have a decreased sugar tolerance during pregnancy. According to Cron, 30 to 50 per cent of pregnant women are less tolerant to glucose than non-pregnant subjects. Again, how frequently do we see the onset of goitre occurring during pregnancy, and also how frequently the further enlargement of an already existing goitre during this period. It is interesting to note that two of the three cases which did not begin at puberty began during the period of gestation.

The mental state during menstruation is most striking. We very frequently have a much changed personality, manifesting itself in melancholia, general irritability and unreasonableness. Women who ordinarily have a very fine and even disposition are very frequently emotional and cry easily. The relation of emo-

tion to epilepsy in bringing on attacks has long since been noted. At least one emotion has, in a measure, been put upon an endocrine basis, in that Cannon has presented evidence that in fear the adrenalin content of the blood is increased. In this group of ten consecutive female cases, the seizures occurred quite universally about this emotional period in seven.

The exact relationship of the endocrine glands to epilepsy, if there be any at all, is at the present time quite hazy. However, Cushing has observed from the study of a series of cases that epilepsy is a frequent accompaniment of clinical conditions in which insufficiency of the hypophyseal gland is manifestly evident. It has never been observed in hyperpituitarism. Horsely, in experimental hypophysectomies in dogs noted that the cerebral cortex was unusually excitable, and Cushing has reported that animals kept for a long time after this operation showed a tendency to epileptiform convulsions. In some cases of epilepsy the administration of hypophyseal extract has served to modify the seizures. These observations would seem to contradict some of the clinical evidence of disturbed endocrine function noted previously in regard to pregnancy. But there is no reason to assume that in every case a disturbance, if present, is in the nature of hyperactivity.

Harrower has put forward some data to show that certain cases are associated with hypothyroidism, and Sajous states that by giving small doses of thyroid he has controlled the seizures as successfully as with bromides.

There is also some evidence that hyperactivity of the adrenals is in some way related to this disease. Benedek was able to produce typical epileptic seizures in seven of nineteen patients subject to epilepsy who were given adrenalin subcutaneously. This has never been observed in other diseases, nor in normal individuals. Also typical epileptic attacks have been produced in rabbits by repeated intravenous injections of adrenalin (Tracy). Bruning has removed the left suprarenal in nine cases of epilepsy. An improvement was effected in all cases, and in two the attacks ceased entirely. However, he wishes it distinctly understood that he does not claim this to be a cure for all cases of epilepsy.

The close relation of the gonads to the other endocrine glands, especially the pituitary and the thyroid, is well known.

After a study of one hundred and fifty thousand seizures, Clark has concluded that we must look for the principle of pathogenesis in an accumulation of waste products. Probably the regulation and restriction of diet, so important in the treatment of this disease, finds its scientific explanation in the consequent lessened catabolism, there being fewer end products to be taken care of. Very little is known as yet of the metabolism in epilepsy, but with the endocrine glands recognized as the regulators of metabolism, it would seem that there is at least a fruitful field for accurate observation and investigation along these lines. Until we have more exact methods of determining histological, gross and functional pathology of these glands and, perhaps, until experimental glandular therapy has advanced further, the exact relationship will naturally remain obscure. It would be unjustifiable to draw any conclusions from so few cases as reported here, but I can see in them hints that point quite definitely to endocrine disturbance being an important factor in the causation of some cases of this disease.

BIBLIOGRAPHY

Benedek, L.: Über die Auslössung von epileptischen Aufällen mit Nebennierenextrakt. Wien. klin. Wchnschr., 1918, **31,** 1365; Abst. Endocrinol., **3,** 349.

Bisgaard, H. & Növig, P.: Fortsatte Undersögelser over Neutralitetsregulation von genuin Epilepsi. Hospitalstid. (Copenhagen), 1920, **63,** 49-62; Abst., Endocrinol., **4,** 677.

Bruning, A.: Die Extirpation der Nebenniere zur Behandlung von Krämpfen. Zentralbl. f. Chir. (Leipz.), 1920, **47,** 1314-1317.

Caro: The incidence of intestinal adhesions as a factor in chronic intestinal stasis in the epilepsies. Bull. Mass. Comm. Ment. Dis. (Boston), 1918-19, **2,** 80-84.

Cron: Glycosuria during pregnancy. Am. J. Obst. & Gynec. (St. Louis), 1920, **1,** 276-287.

Cushing, Harvey: The pituitary body and its disorders; clinical states produced by the hypophysis cerebri. Phila. & Lond., 1912, J. B. Lippincott Co., 251 p. roy. 8° (p. 272).

Dana, Charles L.: Text book of nervous diseases. 4th. ed. N. Y., 1897. Wm. Wood & Co., 623 p. 3 pl. 8° (p. 475).

Erdheim, J. & Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse. Beit. z. path. Anat. v.z. allg. Path. (Jena), 1909, **46,** 1-132, 4 pl.

Harrower, H. R.: The relation of the thyroid gland to epilepsy. Lancet-Clin. (Cincinnati), 1916, **116,** 100-104.

Tracy, E. A.: Fright as a cause of epilepsy, and how it acts. Endocrinol. (Los Angeles), 1920, **4,** 221-228.

White, William A. & Jelliffe, Smith E.: Modern treatment of nervous and mental diseases. Phila. & N. Y., 1913, v. 2, 816 p. 50 pl. 8° (p. 225).

DOES THE ADMINISTRATION OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO THE TADPOLE PRODUCE AN EFFECT SIMILAR TO THAT OBTAINED FROM THYROID FEEDING?*

PHILIP E. SMITH AND GARNETT CHENEY
Department of Anatomy, University of California
BERKELEY

In a recent paper Hoskins and Hoskins (1920)[1] have advanced evidence showing that the feeding of the anterior lobe of the pituitary gives an effect similar to, and perhaps even identical with, that which is characteristic for the administration of thyroid gland. This is the most convincing evidence which to our knowledge has been advanced in support of the hypothesis that the pituitary can act vicariously for the thyroid. Hoskins and Hoskins, in brief, showed that a preparation of the anterior lobe[2] when fed to the tadpole gave the typical responses resulting from thyroid administration, *i. e.*, cutaneous and mouth changes, leg growth, tail absorption, and other changes leading to metamorphosis. In the normal unoperated tadpole metamorphosis was prematurely inaugurated or greatly accelerated; in the thyroidectomized tadpole similar changes were induced, though, as is well known, they would never have otherwise appeared in these thyroidless specimens.

These results furthermore might appear to be partially though not completely in harmony with the findings obtained from the opposite procedure, namely, the ablation of the hypophysis. For, in the mammal, hypophyseal deficiency causes a retention of infantile characteristics, and in the tadpole the loss of the buccal component of the hypophysis results in the retention of the larval condition for the life of the individual. The opposite picture resulted from the feeding experiments of the Hoskins, namely a hastening of development, this presum-

*Aided by a grant from the Research Board of the University of California.

1. This paper appeared subsequently to the untimely death of Dr. Hoskins, by which experimental research in this field has lost a devoted contributor.

2. Anterior lobe tablets prepared by Armour and Company.

ably being due to the presence of an excess of the pituitary secretion in the organism. It might thus appear that the results obtained by the Hoskins could logically be expected, for if the loss of the pituitary inhibits metamorphosis, should not the feeding of this substance accelerate it?

Yet it must be kept in mind that the retention of the larval condition in the hypophysectomized tadpole undoubtedly is not a pure hypophyseal effect. Rather it is polyglandular in nature, for it has been known since Adler's experiments in 1914 that the loss of the pituitary leads to a profound atrophy or underdevelopment of the thyroid, findings which have been amply confirmed in a series of papers by Allen and Smith, while one of us (Smith, 1920) has shown that both components of the adrenal, the parathyroid glands, and the neural lobe of the hypophysis are profoundly affected by hypophysectomy. Of this system of organs, because of the well known metamorphic stimulus afforded by thyroid feeding in amphibia, (Gudernatsch, 1914; Lenhart, 1915; Morse, 1914; and others) it seems reasonable to refer the immediate fault for the failure of the hypophysis-free tadpole to metamorphose more to the atrophy or underdevelopment of the thyroid than to an hypophyseal deficiency.

It thus seems that we may justly implicate the thyroid in being partially if not solely responsible for the persistence of the larval condition in the hypophysis-free larvae, and conversely to suspect that the feeding of anterior lobe substance would not give the reverse of this picture, namely, an acceleration of metamorphosis.

In feeding experiments using thyroidless and hypophysectomized larvae in which for many months the sole food of these animals, aside from a small component of lettuce, was fresh beef anterior lobe, one of us (Smith, 1918, 1920) observed no evidence of metamorphosis. Nor were the normal larvae prematurely metamorphosed in any decisive way. The hypophyseal feeding of Gudernatsch (1914) also failed to show the pronounced results reported by the Hoskins.

The question which has again been raised by the work of the Hoskins is a pertinent one. Their results would appear to be decisive, although at variance with what might logically be

expected, as well as in direct disagreement with similar work of other investigators. It thus seems justifiable to present new evidence and perhaps throw more light upon this much vexed question of the interrelationship of the thyroid and hypophysis.

In the experiments herein detailed both normal and thyroidectomized frog larvae were used. The specimens of each of the series were from a common egg mass and only those individuals were used which had obtained a certain average size. Since the various groups composing each series contained only a comparatively small number of specimens (4-5) statistical treatment is precluded. Yet the results have been so decisive that a larger number of individuals appears unnecessary.

The aquariae used were those described in a previous paper (Smith, 1920). They were supplied with a continuous but small amount of freshly aërated sterilized water. The water supply was carefully regulated so that each container received approximately the same amount, hence avoiding a variable dilution of any hormonal or other principle contained in the rearing dishes. The special substances were supplied the groups daily, the uneaten particles and casts being removed 24 hours later. These special substances furnished the entire food supply of the larvae with the exception of a weekly contribution of ground fresh lettuce.

With the exception of the groups receiving fresh pituitary, fresh muscle and fresh liver, each group of a series received an identical amount by weight of pituitary substance at each feeding. The amounts fed proved to be in excess of the nutritional demands of the larvae.

The results reported by Hoskins and Hoskins from the feeding of the anterior lobe tablets used by them were fully confirmed by our work. Not only was metamorphosis in the normal tadpole prematurely inaugurated and greatly accelerated, but also as in the experience of these investigators metamorphosis was inaugurated in the thyroid-free tadpole by the administration of these tablets.

With equal certainty we also confirmed the results from the feeding of fresh and the dried pituitary prepared in this laboratory, Smith (1918, 1920). And we must also report that both Parke Davis' powder and also Armour's powder gave in general

concordant results.[3] These substances did not decisively hasten metamorphosis in the normal tadpole, nor did they induce any indication of metamorphosis in the thyroidless larvae. These results are shown in the following protocols.

SERIES II. This series was composed of nine groups of normal tadpoles, each group being composed of six specimens. These groups received respectively: (1) Parke, Davis' anterior lobe powder; (2) Armour's anterior lobe powder; (3) Armour's anterior lobe tablets; (4) anterior lobe powder prepared in this laboratory; (5) fresh beef anterior lobe; (6) powdered dried posterior lobe; (7) powdered dried muscle; (8) powdered dried liver; (9) ground fresh liver or muscle. Each group received 0.13 gm. (2 grains) of the dried substance daily. (Each anterior lobe tablet, although weighing five grains, contained but two grains of actual pituitary substance.) The fresh substances were not weighed, but were clearly in excess of the nutritional needs, as indeed was the case also with the dried foods. Measurements were taken every three days; only the following need be given:

June 25—Series started. The average total length of the specimens of the various groups was from 25 to 28 mm. with a hind-leg length of approximately 1 mm.

July 15—The specimens of each of the groups except those of group 3 had grown very considerably, now averaging 29 to 33 mm., with a hind-leg length of 1.5 to 3 mm. The specimens of group 3 averaged 25 mm. (body 10 mm., tail 15 mm.) with a hind-leg length of 3 mm. On June 25th the average length of this group had been 28 mm. The specimens of this group were emaciated, were eating but little and cutaneous and mouth metamorphic changes were evident.

July 24—The last specimen of group 3 was dead. All these specimens showed pronounced metamorphic changes but did not develop legs of normal size nor complete the absorption of the tail. The specimens of the other groups continued to grow, averaging 32 to 36 mm.

July 27-August 23—Development continued until the series was discontinued on August 23. Exclusive of the specimens of group 3 the most rapid development took place in the specimens of groups 2 and 4, the specimens of these two groups metamorphosing somewhat, though not decisively, earlier than those of the other groups.

SERIES III. This series was composed of five groups of thyroidectomized specimens, each group containing 4 specimens. These groups were fed respectively: (1) Armour's anterior lobe tablets; (2) dried anterior lobe prepared in this laboratory; (3) fresh anterior lobe; (4) dried muscle; (5) fresh muscle or liver. The same dosage was used as in Series II. Measurements were taken every three days.

July 1—Series started. The average length of the specimens of the various groups varied from 28.5 to 31 mm. The hind-limb buds were just distinguishable, being about .1 to .2 mm. in length.

July 15—Slight growth had taken place in the specimens of all of the groups except those of group 1. The specimens of group 1 averaged 28 mm. with a hind-leg length of 1.5 mm. The specimens of the other groups averaged from 29.5 to 32 mm. with a hind-leg length of .2 to .4 mm. All specimens were typical thyroidectomized larvæ.

July 24—The specimens of group 1 averaged 26.5 mm. in total length, with a hind-leg length of 3.5 mm. They appeared somewhat

3. These tablets and powders were supplied this laboratory by Armour and Company and by Parke, Davis & Company. We wish to express our appreciation for their cooperation.

emaciated and metamorphic cutaneous, and mouth changes were plainly evident. The specimens of the other groups averaged from 30.5 to 33 mm., with a hind-leg length of .4 to .6 mm. and were typical thyroidectomized larvæ.

August 9—One specimen of group 3 died on August 4. The skin and mouth was of adult type but the absorption of the tail had not been completed. The other members of this group averaged 24 mm. in total length, with a hind-leg length of 4.6 mm. The mouth and skin was of adult type in every member of this group. The specimens of the other groups averaged 34 to 38 mm. in total length, with a hind-leg length of .4 to .7 mm. and were typical thyroidectomized larvæ.

August 19—The specimens of group 1 averaged 19.5 mm. in total length (body 10.6, tail 9), with hind-legs 6 mm. in length. Three specimens had fore-legs and all were of adult shape. The specimens of the other groups averaged from 36 to 44 mm., with hind-legs measuring from .6 to 1 mm. They were typical thyroidectomized larvæ.

August 24—The last specimen of group 1 died on August 22. It was of adult type but the tail was not completely resorbed nor were the legs of normal young adult length. The specimens of the other groups averaged from 37 to 45 mm., with hind-legs measuring from .6 to 1.4 mm. They were typical thyroidectomized larvæ.

Thus the anterior lobe preparations which we have employed are separable into two classes by their ability or lack of ability to decisively stimulate metamorphosis: (1) One substance—the only one employed by the Hoskins—afforded a pronounced metamorphic stimulus. (2) The other substances failed to alter decisively the usual developmental history of the larvae. Which effect, then, expresses most nearly the actual physiological capacity of the gland when employed in feeding experiments with the normal or thyroidless individual?

Since but one anterior lobe preparation gave a pronounced metamorphic stimulus while four preparations, including the fresh gland, failed to give this stimulus, it would appear that the substances of the last mentioned class because of their numerical majority, represent in their action the physiological capacity of the gland when fed to the tadpole.

The problem now entered its second phase. We directed our attention to the determination of any peculiarities, other than physiological, which might be enjoyed by the single substance giving this extreme metamorphic stimulus so unique in hypophyseal feeding.

Because of the known potency of iodine in organic or inorganic form to metamorphose the tadpole (Allen 1919, Swingle 1919), thyroxin iodine being also potent in this respect (Rogoff and Marine 1916) it seemed not improbable that an

analysis for the iodine content of these various preparations would prove suggestive.

Analyses made by Dr. E. C. Kendall showed the iodine content of three of the anterior lobe preparations to be as follows: [4]Sample 1 contained .0228 mg. of iodine per gram; sample 2 contained .0037 mg. of iodine per gram; sample 3 contained .1787 mg. of iodine per gram; or the iodine content of 1 was .002% that of 2, .003% and that of 3, .0178%; in other words, number 3 contained 8 times as much iodine as sample 1 and 48 times as much as sample 2. But since anterior lobe substance composed but two-fifths of sample 3, the remaining three-fifths being milk sugar, therefore, the actual pituitary substance of this sample contained approximately 120 times as much iodine as sample 2.

Using the iodine content of sample 3 as a standard we then prepared three diets (diets 4, 5, 6) each having the precise iodine content of sample 3, and one check diet (diet 7). The supply from which sample 3, above, was taken served as diet 3. These diets were as follows.

Diet 4—"Anatomy pituitary" 2 parts, milk sugar 3 parts, to which thyroxin[5] was added in sufficient amount to give an iodine content of 0.1787 mg. of iodine per gm. (See analysis of 3.)

Diet 5—"Anatomy pituitary" to which thyroxin was added in sufficient amount to give an iodine content of .4467 mg. of iodine per gm. (Diets 3, 4, and 6 were fed in 5 grain doses. Each group then received 2 grains of actual pituitary substance. Diet 5 was fed in 2 grain (0.13 gm.) doses, thus to give an amount of iodine at a feeding equivalent to the other samples it needed to contain 0.4467 mg. of iodine per gm.)

Diet 6—"Anatomy pituitary" 2 parts, milk sugar 3 parts, to which KI was added in sufficient amount to give an iodine content of 0.1787 mg. of iodine per gm.

Diet 7—"Anatomy pituitary" 2 parts, milk sugar 3 parts.

Two critical series, one composed of normal and one of thyroidectomized tadpoles, were fed with diets 3 to 7. We wish to call special attention to the fact that each of the groups in a series contained the same number of animals and that the animals composing these groups were nearly of the same size. (See protocols of Series V and VI.) Further, each group of a series

4. Sample 1 was Armour's anterior lobe powder. Sample 2 was dried anterior lobe substance prepared in this laboratory, "Anatomy pituitary." Sample 3 was Armour's anterior lobe tablets.

5. The thyroxin was kindly supplied the laboratory in crystalline form by Dr. Kendall in 1918. It contained 65% of iodine.

received the same amount of dried pituitary substance and, except for the check group, the same amount of actual iodine, though in different combinations. These two series then would appear to fulfil all the essential requirements for determining whether pituitary plus iodine in certain combinations would give the effect which the Hoskins had secured and which we had confirmed with the substance which they employed, but with no other pituitary substance.

SERIES V. This series was composed of five groups of 4 normal specimens each. These groups received respectively: (1) diet 3; (2) diet 4; (3) diet 5; (4) diet 6; (5) diet 7. Each group, except 3, received daily 0.324 gm. of its special diet; group 3 received two-fifths of this amount or 0.13 gm. daily. Thus each group received an identical amount of pituitary substance. Measurements of body, tail, and leg lengths were taken every three days.

August 27—The series was started. The specimens of the various groups averaged 38 to 40 mm. in total length, with a hind-leg length of 4.5 to 7.5 mm. They were typical larvæ in all respects.

September 7—The specimens of groups 1, 2, and 3 averaged 32 to 35 mm. in total length, with a hind-leg length of 12 to 14.5 mm. The epidermis and mouth of each were assuming the adult type, the tails in a few cases were undergoing resorption. The specimens of groups 4 and 5 averaged 40 mm. in total length, with a hind-leg length of 8.5 to 10 mm. All specimens were typical larvæ.

September 16—The specimens of groups 1, 2, and 3 averaged 23 to 27 mm. (body 13 mm., tail 11 mm.). The fore-legs were out in all specimens and the mouth and skin of each specimen was of adult type. The specimens of groups 4 and 5 averaged respectively 41 and 43 mm. in total length, their hind-legs averaging 16 mm. The fore-legs were not visible. Those of group 5 were typical larvæ; the skin and mouth of each of the specimens of group 4 showed slight metamorphic changes.

September 19—The specimens of groups 1, 2, and 3 were all adult in shape and their tails were nearly resorbed (4 to 8 mm.). Two specimens of group 1, three of group 2, and one of group 3 had completed metamorphosis. The bodies of the specimens of group 4 averaged 14 mm., their tails 21 mm. Fore-legs were out in 3 specimens. The hind-legs of all were of young adult size, the skin was of adult type, and the mouths of 2 specimens were of adult type, while 2 were of larval type. The bodies of the specimens of group 5 averaged 15 mm., the tail 27 mm. The hind-legs were of young adult size, the skin was partly of adult type. One specimen had fore-legs.

September 21—All specimens of groups 1, 2, and 3, had metamorphosed.

September 26—Two specimens of group 4 metamorphosed. The bodies of the two remaining specimens measured 15 mm., the tails 18 mm. All were of adult shape. The bodies of the specimens of group 5 averaged 15 mm., their tails 27 mm. The fore- and hind-legs, mouth and skin were of adult type.

September 29—One young adult removed from group 5.

October 2—The last specimens of groups 4 and 5 metamorphosed.

SERIES VI. This series was composed of 5 groups of 4 thyroidectomized specimens each. These groups were placed under the same

dietary régime as those of Series V., namely: (1) received diet 3 (sample 3); (2) diet 4; (3) diet 5; (4) diet 6; (5) diet 7.

August 26—The series was started. The specimens of groups 1, 2, 4, and 5 averaged 36 to 40 mm. in total length, with a hind-leg length of 0.3 to 0.7 mm. (The specimens of group 3 varied greatly in size and will not be included in the following. Their history varied but little from that of the specimens of groups 1 and 2.)

September 11—The specimens of the various groups averaged from 35 mm. (group 1) to 43 mm. (group 5), those of groups 1 and 2 had hind-limb buds 2 to 2.5 mm. in length, and those of groups 4 and 5 hind-limb buds of 0.5 to 0.7 mm. All specimens were typical thyroidectomized larvæ.

September 19—The specimens of groups 1 and 2 averaged respectively 35 and 39 mm. with hind-legs 3 to 4 mm. in length. Each showed distinct metamorphic changes in its skin and mouth. The specimens of groups 4 and 5 measured respectively 40 and 45 mm. in length, with hind-limb buds 0.6 to 0.9 mm. and were typical thyroidectomized larvæ.

September 29—The specimens of groups 1 and 2 averaged respectively 19 and 34 mm. in total length, with a hind-leg length of 6 to 8 mm. The skin and mouth of each specimen were of adult type. The members of groups 4 and 5 averaged respectively 42 and 47 mm. in total length, with a hind-leg length of 1 to 1.4 mm. and were thyroidectomized typical larvæ.

October 4—Two specimens of group 1 and one specimen of group 2 were nearly transformed and died the following day.

October 7—The remaining specimens of groups 1 and 2 measured respectively: body 11 mm., tail 6 mm., and body 15 mm., tail 10 mm. All had fore-legs and were adult in shape. The specimens of groups 4 and 5 averaged respectively: body 15.5 mm., tail 27 mm., and body 17 mm., tail 32 mm. They had hind-legs 0.6 to 1.2 mm. in length, and were typical thyroidectomized larvæ.

October 13—The remaining specimens of groups 1 and 2 had transformed; they were not typical young adults, but were weak and had shorter legs than normal, especially the members of group 1. The specimens of groups 4 and 5 had a typical larval shape, showed no indications of metamorphic changes and averaged respectively 45 and 51 mm. in length, with hind-limb buds 1 to 1.3 mm.

These two series have furnished concordant and decisive testimony as to the action of these thyroid-pituitary or iodine-pituitary substances. The specimens of the groups receiving anterior lobe plus inorganic iodine paralleled very closely in development and growth their fellows supplied with a diet of anterior lobe only. And we would recall at this point that no decisive deviation resulted from the administration of our dried anterior lobe substance when carefully checked by diets of fresh anterior lobe substance and fresh and dried muscle. Very different results were obtained with the specimens of those groups receiving pituitary plus thyroxin iodine or pituitary mixed with milk sugar plus thyroxin iodine. These specimens paralleled in

development the specimens fed with the "anterior lobe" tablets, the normal tadpoles showing a greatly accelerated metamorphosis, the thyroidectomized larvae an initiation and rapid progression of the metamorphic process.

It now only remains to discuss briefly the results which we have obtained. The interesting and suggestive findings obtained by Hoskins and Hoskins, and which indeed seemed to demonstrate clearly that the thyroid and anterior lobe afforded an identical stimulus to metamorphosis, and thus were here presumably similar in function, appear to have been secured by the administration of "anterior lobe" substance displaying a unique activity. This appears clearly to be the case since the fresh gland and the dried gland secured from three sources failed to give the effects which they report.

Further, the "anterior lobe" substance which gave this thyroid effect was unusual in the amount of iodine which it contained. It will be recalled that an analysis of this substance showed an iodine content of 0.1787 mg. per gm., thus exceeding by some 120 times the amount of iodine which the dried gland prepared in this laboratory contained. However, the iodine content of our pituitary (0.0037 mg. per gm.) is as great as is usually found in anterior lobe substance, for analyses have shown no more than a trace and usually an absence of this halogen, Simpson and Hunter (1911), Denis (1911), Halliburton, Candler and Sikes (1909) and Seaman (1920).

It has repeatedly been shown that the iodine content of the thyroid gland is subject to a seasonal variation, Seidell and Fenger (1913), Fenger (1918). By analogy we might find an explanation for the high iodine content of the material used by the Hoskins if it was shown that there is likewise as great or a greater seasonal iodine variability in the anterior lobe of the pituitary.

We have attempted to ascertain whether anterior lobe substance, to which iodine in certain forms was added in amounts identical with that occurring in the "anterior lobe" tablets which gave this decisive metamorphic stimulus, would likewise give this stimulus. Inorganic iodine (KI) gave negative results, although from the conclusive work of Allen (1919) and Swingle (1918), it is certain that if used in larger amounts it would have induced

metamorphosis. Our results in this respect are somewhat similar to those of Cameron and Carmichael (1920), who found that sodium iodide failed to give any of the metabolic effects (enlargement of heart, liver, kidneys, etc.), which they obtained in the mammal by thyroid feeding even when the iodine was used in amounts 100 times as great as occurred in the thyroid substance used by them. We obtained positive results with iodine in the form of thyroxin iodine in amounts identical with that found in the tablets. The tadpoles supplied with this substance paralleled in development their tablet-fed brethren.

Evidence has been repeatedly advanced suggesting a vicarious relationship between the anterior lobe of the pituitary and the thyroid gland since the pioneer work of Rogowitch in 1888. Such evidence has not clearly established such a vicarious relationship though it cannot be questioned that an inter-relationship obtains between these two glands, as indeed is the case between all the members of the endocrine system. The early removal of the pituitary leads to a striking underdevelopment of the thyroid, Adler (1914), Smith (1916), Allen (1917). There can be thus no assumption of the function of the ablated gland by the thyroid under this condition. It has been assumed that the enlargement of the pituitary subsequent to thyroidectomy, which has been clearly demonstrated by Rogowitch (1888), Trautmann (1916), Rogers (1918), Hoskins and Hoskins (1919), and others, indicated that the pituitary was compensating for the loss of the thyroid. Yet the evidence does not prove that such is the case. From the physiological side the work of Simpson and Hunter (1911) is against this view, while the classical work of Trautmann (1916) shows that although there is a hypertrophy of the anterior lobe following thyroidectomy, yet this hypertrophy ultimately leads to degenerative changes. Ablation experiments thus do not supply evidence of a vicarious relationship between the anterior lobe and the thyroid. Likewise feeding experiments have failed to establish that anterior lobe feeding gives a thyroid effect, or conversely that thyroid feeding gives an hypophyseal effect.

In 1918 one of us, Smith, noted that anterior lobe feeding to the normal tadpole produced a slightly larger individual and a somewhat earlier average appearance of meta-

morphosis and completion of the same. These effects did not exceed the normal variation and so were not decisive. In general these results have been confirmed in the present study though again they have not transcended the normal variation and so have not been decisive. Any earlier metamorphosis was not gained, however, at the expense of the size of the individual as in thyroid feeding; the effects are very dissimilar. These results secured by the administration of anterior lobe to tadpoles appear to be similar to, but not as pronounced as, the very interesting results gained by transplanting the anterior lobe into the normal, pituitaryless or thyroidless tadpole reported by Allen (1920, 1921). This investigator reports that such grafts stimulate growth but "clearly show that the anterior lobe of the hypophysis exerts an influence upon metamorphosis only indirectly through its influence upon the thyroid gland." Clearly, evidence secured from the experimental ablation, feeding, and transplantation of the anterior lobe and of the thyroid have failed to establish that a functional similarity or vicarious relationship exists between these two glands.

SUMMARY

1. We were able to confirm the results of Hoskins and Hoskins obtained by the feeding of what they supposed to be anterior lobe tablets. Tablets of this substance obtained from the same source as their material caused an acceleration of metamorphosis in the normal tadpole and induced metamorphosis in the thyroid-free larvae.

2. Fresh anterior lobe substance, dried anterior lobe prepared in this laboratory, and the dried gland from two other sources failed, on the other hand, to alter decisively the development of the normal tadpole or to induce metamorphosis in the thyroidless specimens.

3. Analyses of these two classes of anterior lobe substances revealed the fact that the substance affording a metamorphic stimulus contained 0.1787 mg. of iodine per gm. (Each gram of this substance was composed of 0.4 gm. of anterior lobe substance and 0.6 gm. of milk sugar. Thus the actual pituitary substance would supposedly have contained 0.4467 mg. of iodine per gm.) The dried anterior lobe substances prepared in this labora-

tory contained approximately 1/120 of this amount of iodine, or 0.0037 mg. per gm.

4. Normal and thyroidectomized tadpoles fed upon the dried anterior lobe substance prepared in this laboratory, to which sufficient iodine in the form of KI to give an iodine content of 0.4467 mg. per gm. was added, nearly paralleled in development the tadpoles receiving the fresh gland and the untreated dried gland. On the other hand, normal and thyroidectomized tadpoles fed upon the dried anterior lobe substance prepared in this laboratory, to which sufficient iodine in the form of thyroxin iodine was added to give an iodine content of 0.4467 mg. per gm., exhibited a rapid rate of metamorphosis, paralleling in their development the tadpoles mentioned in paragraph 1 of the Summary.

LITERATURE CITED

Adler (L.): Metamorphosestudien an Betrachierlarven. Arch. f. Entwcklngsmechn. (Berl.), 1914, **39**, 21-45.

Allen (B. M.): Effects of the extirpation of the anterior lobe of the hypophysis of Rana pipiens. Biol. Bull. (Woods Hole), 1917, **32**, 117-130.

Allen (B. M.): The relation of the pituitary and thyroid glands of Bufo and Rana to iodine and metamorphosis. Biol. Bull. (Woods Hole), 1919, **36**.

Allen (B. M.): Experiments in the transplantation of the hypophysis of adult Rana pipiens to tadpoles. Science (Garrison, N. Y.), N. S., 1920, **52**, 274-276.

Allen (B. M.): The effects of transplantation of the several parts of the adult hypophysis into tadpoles in Rana pipiens. Proc. Am. Soc. Zool., Anat. Rec. (Phila.), 1921, **20**, 192-193.

Cameron (A. T.) & Carmichael (J.): Contributions to the biochemistry of iodine. III. The comparative effects of thyroid and iodide feeding on growth in white rats and in rabbits. J. Biol. Chem. (Balt.), 1920, **45**, 69-100.

Denis (W.): A note regarding the presence of iodine in the human pituitary. J. Biol. Chem. (Balt.), 1911. **9**, 363-364.

Fenger (F.): On the seasonal variations in the iodine content of the thyroid gland. Endocrinology (Los Angeles), 1918, **2**, 98-100.

Graham (A.): A study of the physiological activity of adenomata of the thyroid gland, in relation to their iodine content, as evidenced by feeding, experiments on tadpoles. Jour. Exp. M. (Balt.), 1916, **24**, 345-359.

Gudernatsch (J. F.): Feeding experiments on tadpoles. Am. Jour. Anat. (Phila.), 1914, **15**, 431-480.

Halliburton (W. D.), Candler (J. P.) & Sikes (A. W.): The human pituitary body. Quart. Jour. Exp. Physiol. (Lond.) 1909, **2**, 229-242.

Hoskins (E. R.) & Hoskins (M. M.): Growth and development of amphibia as affected by thyroidectomy. Jour. Exp. Zool. (Phila.), 1919, **29**, 1-69.

Hoskins (E. R.) & Hoskins (M. M.): The inter-relation of the thyreoid and hypophysis in the growth and development of frog larvae. Endocrinology (Los Angeles), 1920, **4**, 1-32.

Lenhart (C. H.): The influence upon tadpoles of feeding desiccated thyroid gland in variable amounts and of variable iodine contents. Jour. Exp. M. (Balt.), 1915, **22**, 739-746.

Morse (M.): The effective principle in thyroid accelerating involution in frog larvae. J. Biol. Chem. (Balt.), 1914, **19**, 421-429.

Rogers (J. B.): The effect of the extirpation of the thyroid upon the thymus and the pituitary glands of Rana pipiens. Jour. Exp. Zool. (Phila.), 1918, **24**, 589-605.

Rogoff (J. M.) & Marine (D.): Effect on tadpoles of feeding products obtained by alkaline hydrolysis. J. Pharm. & Exp. Therap. (Balt.), 1916, **9**, 57-73.

Rogowitch (N.): Sur les effets de l'ablation du corps thyroide chez les animaux. Arch. de Physiol. (Paris), 1888, Série 4, **2**, 419-467.

Seaman (E. C.): Note on the presence of iodine in large quantities of sheep pituitary gland. J. Biol. Chem. (Balt.), 1920, **43**, 1-2.

Seidell (A) & Fenger (F.): Seasonal variation in the iodine content of the thyroid gland. J. Biol. Chem. (Balt.), 1913, **13**, 517-526.

Simpson (S.) & Hunter (A.): The possible vicarious relationship between the pituitary and thyroid glands. Quart. Jour. Exp. Physiol. (Lond.), 1911, **4**, 257-272.

Smith (P. E.): The effect of hypophysectomy in the early embryo upon the growth and development of the frog. Anat. Rec. (Phila.), 1916, **11**, 57-64.

Smith (P. E.): The growth of normal and hypophysectomized tadpoles as influenced by endocrine diets. Univ. Cal. Pub. in Physiol. (Berkeley), 1918, **5**, 11-22.

Smith (P. E.): The pigmentary, growth and endocrine disturbances induced in the anuran tadpole by the early ablation of the pars buccalis of the hypophysis. Amer. Anat. Mem. (Phila.), 1920, No. **11**.

Swingle (W. W.): Iodin as the active principle of the thyroid gland. Endocrinology (Los Angeles), 1918, **2**, 283-288.

Swingle (W. W.): Studies on the relation of iodin to the thyroid. Jour. Exp. Zool. (Phila.), 1919, **27**, 397-415.

Trautmann (A.): Hypophyse und Thyreoidektomie. Frankfurter Ztschr. f. Path., 1916, **80**, 173-305.

THE INTERNAL SECRETION OF THE SPLEEN

NATHAN B. EDDY

(From the Department of Physiology and Biochemistry, University of Alberta)

EDMONTON, CANADA

A wide variety of functions has been assigned to the spleen from time to time, most of them involving the life cycle of the blood corpuscles. It has been claimed, for instance, that new red blood corpuscles are formed in the spleen, also that red corpuscles are destroyed in this organ. Others have claimed that the spleen produces white blood corpuscles and still others that it is a place where white corpuscles are destroyed. The investigations in support of these hypotheses have consisted of histological examination of the splenic tissue and comparative counts of the corpuscles in the blood entering and leaving the spleen. Large numbers of blood corpuscles of all sorts are found in the spleen, but their presence can be explained just as well on other grounds than that they are being produced there. The reports on the corpuscle content of the blood to and from the spleen are very conflicting. Malassez and Picard (25), Emelianow (12) and Morris (26) report more erythrocytes in the blood of the splenic vein than in that of the artery; Virchow (44) and Frey (13) report fewer in the venous blood; Vulpius (45), Paton, Gulland and Fowler (31) and Freyer (14) find no difference in the red corpuscle content of the blood entering and leaving the spleen. Similarly divergent reports have been made in regard to the white corpuscles. According to Funke and Hirt (16), Gibson (18), Grigorescu (19), Emelianow (12), Bulgak (6) and Morris (26) the leucocytes are increased in the blood leaving the spleen; Vulpius (45) and Paton, Gulland and Fowler (31) found the number of white corpuscles in the venous blood decreased; no noteworthy difference in the leucocytes of splenic artery and vein were detected by Tarchanoff and Swaen (43), Virchow (44) and Freyer (14). One concludes, therefore, that probably the adult spleen normally contributes no new formed elements

to the blood, and that it does not continually remove any significant number of corpuscles from the circulation.

The blood corpuscles, both red and white, are produced chiefly in the red marrow of the bones. Both are destroyed in all parts of the blood stream. According to Robertson and Rous (38) the mechanism of destruction of the old erythrocytes is a process of fragmentation with more or less dissolution of the particles in the blood stream. The fragments are removed from the circulation by the spleen, assisted possibly by the liver and red bone marrow. Such phagocytic power of the spleen for the corpuscular debris has been clearly demonstrated by these authors and by Tait and McCartney (42) for other foreign matter, Indian ink and powdered quartz. The latter also demonstrated similar ability on the part of the liver and bone marrow to remove from the circulation the foreign matter injected. They pointed to the existence of sinusoids in all three organs as a significant point of similarity. The spleen removes the fragments of the corpuscles from the blood not only because they are no longer of any use in the circulation of the organism, but probably also because the cells of the spleen in some way elaborate this material as a step in the production of body pigments and for re-utilization by the bone marrow in the manufacture of new corpuscles.

Another theory is that the spleen produces an internal secretion which regulates the number of corpuscles, particularly erythrocytes, in the circulating blood. Such an internal secretion might stimulate or depress the activity of the bone marrow; it might facilitate the fragmentation or dissolution of the old corpuscles; or, it might alter the number of corpuscles in active circulation by altering their distribution.

The existence of an internal secretion and its physiological action may be demonstrated by (1) the specific effects following congenital deficiency or experimental removal, (2) the symptoms noted in cases of hyperplasia of the organ, presumably accompanied by hypersecretion, (3) the administration of the substance of the gland or an extract, either in the absence of the gland when it might ameliorate the symptoms due to removal, or, when the organ is present, to simulate hypersecretion. One has to assume, of course, the existence in the preparations em-

ployed, gland substance or extract, of the active principle of the secretion of the living cells. In our own experiments we have employed the method of injection of splenic preparations.

Some of our experiments in this connection have been reported elsewhere (10). The technique and results are in part as follows:

Rabbits were used exclusively. Specimens of blood were taken simultaneously for counting both red and white corpuscles. After an initial corpuscle count the desired dose of splenic preparation was injected subcutaneously. Subsequent red and white corpuscle counts were made at half hour intervals during the first two or three hours after injection and a final count was made four or five hours from the beginning of the experiment.

In the first ten experiments the preparation employed was powdered dried spleen, prepared by Armour & Company. The dose of 10 mgm. per kilogram of body weight of the rabbit was dissolved in about 2 cc. of physiological saline solution, warmed to 37°C. and injected subcutaneously. In each of these experiments there occurred a slight reduction in the red corpuscle count (5.88 per cent) of short duration (69 minutes), and a prompt reduction in the number of white corpuscles followed in several hours by a considerable leucocytosis. The change in the leucocyte count was identical with the effect described by Wells (47) and others as following upon the subcutaneous injection of any foreign protein and was not a specific effect of spleen because it did not occur after the administration of a protein-free preparation.

A protein-free preparation was obtained by pouring a watery solution of the powdered dried spleen (Armour & Company) into absolute alcohol, filtering off the precipitate and evaporating the filtrate to dryness on a water bath. In a second series of ten experiments this residue was used in the dose of 10 mgm. per kilogram of body weight of the rabbit.

Again the red corpuscle count was decreased following the injection, the decrease in these experiments being much more marked (18.68 per cent) and more persistent (102 minutes) than in the first series. Instead of the characteristic effect of foreign protein injections on the white corpuscles an increased leucocyte count of brief duration was recorded in every experiment oc-

curring at or about the time of maximum decrease of the red corpuscles.

We also made fresh extracts of the spleen of dogs and cats. The fresh spleen was ground with sand and macerated overnight in the cold with twice its bulk of physiological saline solution. The preparation was then strained through muslin and filtered. The filtrate was poured in a thin stream into absolute alcohol, the precipitate filtered off and the alcoholic filtrate evaporated to dryness on the water bath. Five experiments were performed in each of which 10 mgm. of the extract of dog's spleen per kilogram of body weight were injected subcutaneously, and two experiments in each of which a similar dose of extract of cat's spleen was administered. In both groups of experiments there occurred a decrease in the red corpuscle count similar to that described following the administration of the splenic preparations (Armour & Company). Furthermore, in the experiments with extract of dog's spleen a transient increase in the leucocytes appeared at about the time the red corpuscles were decreasd to the greatest extent.

The averages of the results obtained in these experiments are shown in table 1. They establish the presence in the splenic preparations of an agent capable of reducing by some means the number of red corpuscles in the circulating blood. Using larger doses, 20 and 40 mgm. of the extract of dog's spleen per kilogram of body weight, the effect of the splenic preparation was not entirely progressive (see Table 1), but further consideration will be given to this point later.

In order to determine whether the decrease in the number of red corpuscles in the circulating blood was the result of the destructive action exerted by the splenic agent on the corpuscles, specimens of blood from an ear vessel of a rabbit were obtained simultaneously in two hemacytometer pipettes in the usual manner. The blood in one pipette was then diluted with 0.7 per cent sodium chloride solution, while the blood in the other was diluted with 0.7 per cent sodium chloride solution in which was dissolved fresh extract of dog's spleen in definite amount. Several successive drops from each pipette were counted and the counts from each averaged and compared. We made determinations using dilutions of 20, 40, 80 and 120 mgm. of fresh extract of dog's

TABLE 1

Decrease in erythrocyte count following subcutaneous injection of splenic preparations.

Number of Observations	Preparation	Dose per Kilo of Body Weight Mgm.	Initial Count	Minimal Count	Amount of Decrease	Percentage Decrease	Minimum in Minutes	Duration of Effect Minutes
10	Powdered dried spleen (Armour & Company)	10	6,877,500	6,471,200	406,300	5.88	45	69
10	Protein-free splenic preparation (Armour & Company)	10	6,635,600	5,396,000	1,239,600	18.68	66	102
5	Extract of dog's spleen	10	6,560,000	5,145,000	1,415,000	21.47	54	144
2	Extract of cat's spleen	10	6,284,000	5,388,000	896,000	14.20	30	75
5	Extract of dog's spleen	20	7,545,200	5,153,600	2,391,600	31.02	90	162
5	Extract of dog's spleen	40	6,879,200	5,236,000	1,643,200	23.88	74	134

spleen per 100 cc. of 0.7 per cent sodium chloride solution. A considerable decrease in the red corpuscle count, which can hardly be explained in any other way than as a direct hemolytic effect of the splenic extract, was obtained. Also the effect was progressive so far as these observations go.

As control further determinations were made in which other tissue extracts were dissolved in the sodium chloride solution used as diluting fluid. Fresh muscle extract (dog), prepared by exactly the same method that we used in making the fresh extract of dog's spleen, and dried acid extract of secretin, prepared by the method previously described (11), were employed. Each was dissolved in the 0.7 per cent sodium chloride solution in the proportion of 40 mgm. per 100 cc. The procedure followed was exactly the same as when we used the splenic extract. The results of these experiments, together with the results obtained with splenic extract in like dilution, are shown in Table 2.

TABLE 2

Control Observations on in vitro Hemolysis.

Blood diluted with normal saline	Blood diluted with normal saline plus tissue extract	Tissue extract employed
5,608,000	5,616,000	Muscle extract (dog).
5,120,000	5,184,000	" "
5,670,000	5,296,000	" "
6,910,000	6,960,000	" "
5,502,000	5,554,000	" "
6,288,000	6,096,000	Secretin preparation.
5,360,000	5,601,000	" "
5,920,000	6,200,000	" "
5,392,000	5,408,000	" "
5,470,000	5,120,000	" "
8,296,000	6,560,000	Extract of dog's spleen.
6,728,000	6,536,000	" " "
5,408,000	5,008,000	" " "
5,808,000	4,952,000	" " "
7,208,000	6,104,000	" " "

It will be seen that the variations in the counts when using muscle extract or secretin preparation are within the range of experimental error of blood counts in general and with neither was any evidence of hemolysis obtained. We conclude, therefore, that the hemolysis caused by the splenic preparation is specific and not a property of foreign tissue extracts.

A number of investigators have sought for direct hemolytic action of splenic extracts outside the body. Nolf (29), Weil (46), Banti (2) and Furno (17) obtained positive results, but Achard, Foix and Salin (1), Widal, Abrami and Brule (48)

and Krumbhaar and Musser (23) were unable to detect any direct hemolytic action of fresh extract of spleen. In these observations, all of which appear to have been macroscopic only, the splenic extract was allowed to act upon washed red corpuscles rather than whole freshly drawn blood. Washing erythrocytes with salt solution, according to Olson (30), may result in the destruction of some of them. It is probable that washing the corpuscles removes the weaker ones and retains only the more resistant, which the splenic substance is unable to destroy. If the hemolytic substance in the extract of the spleen is capable of attacking the less resistant corpuscles only we can understand how it was that in the experiments just quoted no hemolysis was observed, whereas in our experiments, in which fresh whole blood was used, a marked diminution in the number of red corpuscles took place. The authors who obtained no hemolysis with their splenic preparations argued that the hemolytic substance sometimes observed was produced on standing by bacterial action in the watery extracts. As pointed out, we used for these in vitro experiments fresh extract of dog's spleen and we believe our method of procedure would reduce to a minimum the possibility of bacterial action.

Brinchmann (4) finds that feeding normal rabbits and guinea-pigs with fresh ox spleen leads to a considerable reduction in the red and white corpuscles. These effects are not produced by feeding other raw flesh of identical iron content.

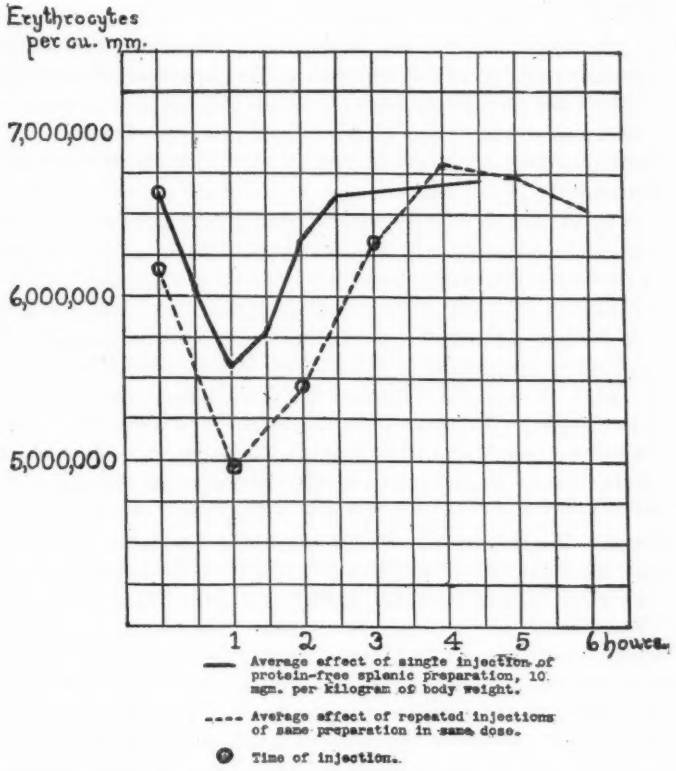
Zelenski (49) in 1891 and Danilewski (8) in 1895 were able to cause a marked increase in the number of red corpuscles in the circulating blood and also in the hemoglobin content of the blood following a single intraperitoneal injection of splenic extract. Paton, Gulland and Fowler (31) repeated their experiments without being able to detect any change in the erythrocytes. Silvestri (39) believed that he obtained an increase in the red corpuscle content of the blood in anemia by the use of injections of splenic extract. Krumbhaar and Musser (23) also were able to bring about an increase in the erythrocyte count and hemoglobin content by the injection of fresh splenic extract. This increase lasted one or two days and could be reobtained by repeating the dose.

In each of these cases a blood count was not made until the day following the injection, whereas our counts were begun immediately after the injection and continued at short intervals for several hours. It was at this time that the decrease noted by us occurred (see Table 1 for duration of effect). However, we have noted that when an animal was used for a second experiment after the lapse of a few days its initial red corpuscle count was frequently higher than it had been before any of the extract was administered.

The bone marrow usually responds to a lowering by hemorrhage or other means of the number of corpuscles in the circulating blood by increased production of new corpuscles so that, in the present instance, where the immediate effect of the splenic agent is a destruction of the erythrocytes, it is reasonable to expect subsequently increased production. This compensation might very possibly exceed the loss especially if, as has been claimed by Stradomsky (40), the product of splenic activity, in addition to acting directly to destroy red corpuscles, exerts a stimulating influence on the bone marrow. The results obtained in the group of experiments in which 40 mgm. of splenic extract per kilogram of body weight were injected subcutaneously are in accord with this idea of compensatory action on the part of the bone marrow. In this series of experiments the percentage decrease and the duration of effect were both less than when the dose was only 20 mgm. per kilogram (see Table 1). It is possible that the greater the amount of hemolytic agent present the more marked and more prompt is the compensating response. It is more probable that Stradomsky's idea is correct and that the stimulating element of the splenic extract becomes predominant in the larger doses where it is undoubtedly combined with the independent effort of the bone marrow to replace the corpuscles that are being rapidly destroyed.

This interpretation is further borne out by the results obtained when the dose of splenic extract is repeated at short intervals. In ten experiments we have given four doses of 10 mgm. of splenic extract per kilogram of body weight at hourly intervals and followed the changes in the erythrocyte count. We used the protein-free splenic preparation (Armour & Company). In the accompanying chart we have plotted the average result of the

repeated injections (dotted line) and the average change in the number of red corpuscles following a single injection of the same preparation in the same dose (solid line). In both there occurred a sharp decline in the count, but the repetition of the dose caused a prompt restoration of the number of corpuscles in circulation and a rise in the count above the original level. Three



hours after the last injection the count was still above the original.

It is worthy of note that in this series of experiments the leucocyte count increased after the first dose, as it did in the other experiments following a single injection, and frequently

remained elevated until some time after the last dose. Two explanations of the effect of the injections upon the white corpuscle count may be suggested. The increased number of white corpuscles may be evidence of the direct stimulating influence of the splenic hormone upon the bone marrow, or the leucocytes in circulation may be increased to assist by their phagocytic power the removal of the debris of the red corpuscles being destroyed by the splenic agent.

It is possible that the falling off in the erythrocyte count described may be due to a depression of the hematopoietic activity of the bone marrow by the splenic extract, or to a temporary withdrawal of red corpuscles from the circulation. Such assumptions, however, are unsupported by any evidence of which we are aware.

In 1912 Musser (27) reviewed the clinical and experimental observations which had been made to that date upon the changes in the blood following splenectomy. He says, "A general analysis shows that in the majority of cases a marked leucocytosis is present and persists for a year or more; often a pronounced secondary anemia occurs, in which the color index is normal as a rule." A little later Musser and Krumbhaar (28) followed the changes in the blood after splenectomy in seven dogs and found that anemia usually developed quickly and reached its height in from 3 to 6 weeks and then with gradual improvement the blood picture approached the normal after about 3 to 4 months. Accompanying this a marked leucocytosis was observed reaching its height in twenty-four hours but persisting to a slight degree for several months. Variations occurred, but they say, "The anemia is inevitable, as is also, later, some degree of repair." Pugliese (37) found a marked fall in the number of red corpuscles per cubic millimeter of blood followed splenectomy but says the reduction is temporary, less than two months. Hitzrot (21) reported six cases of splenectomy for traumatic rupture of the organ in patients otherwise apparently normal and in all he found a considerable decrease in the red blood corpuscles and an increase in the white corpuscles followed the operation. Tachigara and Takagi (41) compared the effects of splenectomy in young and old animals (dogs) and found that in general the results were the same. They noted a striking

increase in the number of nucleated red blood corpuscles in circulation. The total number of erythrocytes was decreased and there occurred a leucocytosis. Most investigators who have studied the blood changes after splenectomy have found that erythroblasts occur in the circulation only very exceptionally; occasionally they are seen as the animal begins to recover from the anemia.

Botazzi (3), Domenici (9), Brissaud and Bauer (5), Pel (36), Pearce and others (33, 34, 22) found that accompanying the anemia there was a very definite increase in the resistance of the erythrocytes to hemolysis, both by hypotonic salt solution and specific hemolytic immune serum. Fukushima (15) noted that the resistance of erythrocytes to hemolytic toxin produced by poisonous vipers was increased the third day after splenectomy. This increased resistance persisted four to eight weeks and then became normal or slightly subnormal. Karsner and Pearce (22) were able to show that the increased resistance is not due to the accumulation in the blood after removal of the spleen of hemolytic or anti-hemolytic bodies, but is dependent upon changes in the erythrocytes. The degree of resistance appeared to them to increase with the length of time that had elapsed after splenectomy.

Pearce and others (32, 35) examined histologically the liver, lymph nodes and bone marrow in normal and splenectomized dogs. In both the liver and lymph nodes proliferation of endothelial cells phagocytic for red corpuscles followed the removal of the spleen. This was apparently compensatory to the lost phagocytic function of the spleen. The changes in the lymph nodes suggest the idea that the leucocytosis also is a compensatory reaction to assist the removal from the circulation of the disintegrating red corpuscles. It is most marked immediately after the ablation of the spleen and gradually disappears as the changes in the liver and lymph nodes take place.

In the bone marrow there usually occurred, according to the authors quoted (35), a transformation of the fatty marrow of the long bones to a richly cellular red marrow. The change in the marrow is very gradual, not attaining completeness for six to twenty-two months. The change would seem not to be compensatory either to the post-operative anemia or to possible

hemolysis in the lymph nodes. The possibility suggests itself that it may be associated with the taking over by the bone marrow of the function of storing and elaborating the material derived from old corpuscles for purposes of re-utilization. As this function becomes developed it might constitute a stimulus to erythrogenesis and thus aid in the recovery from the anemia. The demonstration by Tait and McCartney (42) of the ability of the bone marrow to remove other foreign material from the circulation has already been mentioned. It is at least conceivable that the bone marrow might similarly remove fragmented corpuscles.

These observations on the histological changes in the bone marrow, liver and lymph glands have been confirmed by Henn (20), who also noted anemia, leucocytosis and increased resistance of erythrocytes in the animals from which the spleen had been removed.

As a control experiment Krumbhaar and others (24) diverted the venous drainage of the spleen. They ligated the splenic vein or transplanted it into the vena cava or established an Eck fistula. The result was an anemia similar to that produced by splenectomy, but on the whole of less grade and duration. An increase in the resistance of the red corpuscles, likewise less marked and less prolonged, and a leucocytosis were also noted.

Burkett (7) performed similar operations for diversion of the splenic blood from the portal circulation. The most striking change in the peripheral blood which he found to follow the operation was the leucocytosis, "Without," he says, "any special change in hemoglobin or the red blood cells which had a normal appearance in fresh blood films." However, he gives figures for two of the five dogs used and in both there was some reduction of the erythrocyte count (12.5 per cent in one of the dogs during the fourth week).

Krumbhaar (24) makes the suggestion that diversion of the splenic blood causes anemia because the internal secretion of the spleen, exerting a stimulating influence on the distant hematopoietic organs, has to be activated in the liver. It is also possible that mechanical modification of the volume of the blood

going to the liver may alter the activity of the liver so as to produce the effects described.

In conclusion, the hypothesis that the spleen produces an internal secretion is supported by (1) the changes in the erythrocytes after splenectomy, (2) the modification of the blood picture in hyperplasia of the spleen, ameliorated in some cases at least by splenectomy, and (3) the specific effects on the red blood corpuscles of injection of splenic extract.

We know nothing of the chemical nature of the supposed splenic hormone and it is difficult to formulate a consistent theory of its possible mode of action. We should like, however, to make the following suggestions: That the chief function of the spleen is the removal from the circulation of the disintegrated erythrocytes; that the splenic cells elaborate this material producing thereby an internal secretion, which was a component of the erythrocyte either stroma or pigment portion; that this internal secretion reduces the resistance of all the red blood corpuscles, the effect amounting to actual destruction of the older cells; and, finally, that this internal secretion, possibly after modification by the liver, stimulates the erythrogenic function of the bone marrow and is used up in the manufacture of new corpuscles.

BIBLIOGRAPHY

1. Achard (C.), Foix (C.) & Salin (H.): Sur le pouvoir hémolytique de l'extrait de rate. Compt. rend. soc. d. biol. (Paris), 1912, **72**, 394.
2. Banti (G.): La Splénomégalia émolitica, anémopiética. Sperimentale, Arch. di biol. (Firenze), 1913, **67**, 323.
3. Botazzi: La Milza come Organo Emocatatonistico. Sperimentale, Arch. di biol. (Firenze), 1894, **48**, 433.
4. Brinchmann (A.): Ueber Veränderungen im Blute von Meerschweinchen und Kaninchen hervorgerufen durch Fütterung mit frischer Ochsmilz. Acta med. Scand. (Stockholm), 1920, **52**, 689.
5. Brissaud & Bauer: Récherches sur la résistance des globules rouges chez le lapin. Compt. rend. soc. d. biol. (Paris), 1907, **62**, 1068.
6. Bulgak (J.): Ueber die Contractionen und die Innervationen der Milz. Virchow's Arch. f. path. Anat. (etc.), (Berl.), 1877, **69**, 181.
7. Burkett (W. C.): Changes in the peripheral blood consequent upon the diversion of the splenic blood into the general circulation. J. Exper. M. (Balt.), 1917, **26**, 849.
8. Danilewski (B.): Ueber die blutbildende Eigenschaft der Milz und des Knochenmarks. Arch. f. d. ges. Physiol. (Leipz.), 1895, **61**, 264.
9. Domenici: Sur l'histologie de la rate à l'état normal et pathologique. Arch. d méd. exper. et d. anat. path. (Paris), 1901, **13**, 1.
10. Downs (A. W.) & Eddy (N. B.): The influence of splenic extract on the number of corpuscles in the circulating blood. Am. J. Physiol. (Balt.), 1920, **51**, 279.
11. Downs (A. W.) & Eddy (N. B.): The influence of secretin on the number of erythrocytes in the circulating blood. Am. J. Physiol. (Balt.), 1917, **43**, 415.
12. Emelianow (P.): Sur le rôle de la rate au point de vue de la composition morphologique du sang. Arch. d. sc. biol. d. St. Petersbg., 1893, **2**, 135.
13. Frey: Erythrocyten Vernichtungswirkung der Milz. Deutsches Arch. f. klin. Med. (Leipz.), 1920, **133**, 223.

14. Freyer (M.): Ueber die Betheiligung der Milz bei der Entwickelung der rothen Blutkörperchen. Inaug. Diss. Königsburg, 1872.
15. Fukushima (A.): Resistance of red corpuscles to the haemolysin of Trimeresus and Agistroden after excision of the spleen and after ligature of the splenic vein. Chugai Iji Shinpo (Tokyo), 1918, **908**, 63; Jap. med. lit. (Seoul), 1920, **5**, 3; Physiol. Abst. (Lond.), 1920, **5**, 289.
16. Funke & Hirt: Quoted by Tarchanoff and Swaen, Arch de physiol. norm. et path. (Paris), 1875, **2**, 324.
17. Furno (A.): Ricerche sperimentali ematologiche, edanatomopatalogische intorno all' emolisi do siero, negli animali normali e splenectomizati. Sperimentale, Arch. di biol. (Firenze), 1913, **67**, 639.
18. Gibson (J. L.): The blood-forming organs and blood formation. An experimental research. J. Anat. & Physiol. (Lond.), 1885, **20**, 100.
19. Grigorescu: Modifications du sang par le séjour prolongé expérimentalement dans la rate. Compt. rend. soc. d. biol. (Paris), 1887, **39**, 548.
20. Henn (S. C.): The effect of splenectomy upon growth in the young. Am. J. Physiol. (Balt.), 1920, **52**, 562.
21. Hitzrot (J. M.): Effects of splenectomy. Ann. Surg. (Phila.), 1918, **67**, 540.
22. Karsner (H. T.) & Pearce (R. M.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. IV. A study, by the methods of immunology, of the increased resistance of the red blood corpuscles after splenectomy. J. Exper. M. (Balt.), 1912, **16**, 769.
23. Krumbhaar (E. B.) & Musser, Jr. (J. H.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. X. Concerning the supposed regulatory influence of the spleen in the formation and destruction of erythrocytes. J. Exper. M. (Balt.), 1914, **20**, 108.
24. Krumbhaar (E. B.), Musser, Jr. (J. H.) & Peet (M. M.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. XIV. Changes in the blood following diversion of the splenic blood from the liver. A control study of the effects of splenectomy. J. Exper. M. (Balt.), 1916, **23**, 87.
25. Malassez & Picard: Recherches sur les fonctions de la rate. Compt. rend. Acad. d. sc. (Paris), 1875, **81**, 984.
26. Morris (D. H.): The role of the spleen in blood formation. J. Exper. M. (Balt.), 1914, **20**, 379.
27. Musser, Jr. (J. H.): An experimental study of the changes in the blood following splenectomy. Arch. Int. Med. (Chicago), 1912, **9**, 592.
28. Musser, Jr. (J. H.) & Krumbhaar (E. B.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. VI. The blood picture at various periods after splenectomy. J. Exper. M. (Balt.), 1913, **18**, 487.
29. Nolf (P.): Le pouvoir autohemolytique du suc de la rate. Compt. rend soc. d biol. (Paris), 1912, **72**, 121.
30. Olson (G. M.): Traumatic haemolysis. J. Lab. & Clin. M. (St. Louis), 1920, **5**, 259.
31. Paton (N.), Gulland (G. L.) & Fowler (J. S.): The relationship of the spleen to the formation of the blood corpuscles. J. Physiol. (Lond.), 1902, **28**, 83.
32. Pearce (R. M.) & Austin (J. H.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. V. Changes in the endothelial cells of the lymphnodes and liver in splenectomized animals receiving haemolytic serum. J. Exper. M. (Balt.), 1912, **16**, 780.
33. Pearce (R. M.), Austin (J. H.) & Krumbhaar (E. B.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. I. Reactions to hemolytic serum at various intervals after splenectomy. J. Exper. M. (Balt.), 1912, **16**, 363.
34. Pearce (R. M.), Austin (J. H.) & Musser, Jr. (J. H.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. III. The changes in the blood following splenectomy and their relation to the production of hemolytic jaundice. J. Exper. M. (Balt.), 1912, **16**, 758.
35. Pearce (R. M.) & Pepper (O. H. P.): The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. IX. The changes in the bone marrow after splenectomy. J. Exper. M. (Balt.), 1914, **20**, 19.
36. Pel (L.): Ueber die Resistance der roten Blutkörper gegenüber hypotonischen Kochsalzlösungen bei entmilzten Hunden. Deutsches Arch. f. klin. Med. (Leipz.), 1912, **106**, 592.
37. Pugliese (A.): Das Eisen der Galle und des Blutes bei entmilzten Tieren. Biochem. Ztschr. (Berl.), 1913, **52**, 423.

38. Robertson (O. H.) & Rous (P.): Fate of erythrocytes. I. In healthy animals. II. In plethoric and anaemic animals. J. Exper. M. (Balt.), 1917, **25**, 651, 665.

39. Silvestri (T.): Milza e eritropoiesi. Patologica (Geneva), 1913, **5**, 145.

40. Stradomsky (B. N.): On the influence of the spleen upon the blood producing capacity of bone marrow. Russk. Vrach (Petrograd), 1916, **15**, 1122.

41. Tachigara (S.) & Takagi (T.): Ueber die Erythroblastose und die Blutveränderung nach der Milzextirpation beim neugeborenen Hunde. Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1917, **17**, 563.

42. Tait (J.) & McCartney, (Mrs. J. E.): The fate of foreign particles injected into the blood stream. J. Physiol. (Lond.), 1919, **53**, Proceedings, xxii.

43. Tarchanoff & Swaen: Des globules blancs dans le sang des vaisseaux de la rate. Arch. d. physiol. norm. et path. (Paris), 1875, **2**, 324.

44. Virchow (R.): Zur pathologischen Physiologie des Blutes. Die Bedeutung der Milz- und Lymphdrüsen-Krankheiten für die Blutmischung. Virchow's Arch. f. path. Anat. (etc.), (Berl.), 1853, **5**, **43**.

45. Vulpius (O.): Beiträge zur Chirurgie und Physiologie der Milz. Beiträg. z. klin. chir. (Tubing.), 1894, **11**, 633.

46. Weill (O.): Hémolyse locale et hémolyse splénique. Trav. d. lab. d. l'inst. Solvay, 1913, **12**, 180.

47. Wells (C. W.): Leukopenia and leukocytosis in rabbits. J. Infect. Dis. (Chicago), 1917, **20**, 219.

48. Widal (F.), Abrami (P.) & Brulé (M.): Apropos du rôle hémolytique de la rate normale. Compt. rend. soc. d biol. (Paris), 1912, **72**, 694.

49. Zelenski: Quoted by Luciani, Human Physiology (Lond.), 1911, **1**, 552.

Editorials

ENDEMIC GOITER: ITS PREVENTION AND TREATMENT

That there are regions in which a high frequency of enlargement of the thyroid gland is observable in the population is a matter of common knowledge. In this country the Great Lakes goiter belt has long been known. A recent statistical study by Levin of the incidence and distribution according to sex and age of one portion of this district is of more than passing interest when correlated with the results of Marine and Kimball on the prevention of goiter in another part of the same general territory. Levin examined, without selection, 1783 persons and found thyroid enlargement in 1146 of the group coming under observation. That is to say a trifle over 64 per cent of the population showed evidence of an actual or potential pathological condition of the thyroid.

The simple goiter incidence, which Levin is inclined to attribute more to a physiological response to an unfavorable environment rather than to an immediate pathological state, though he points out that such enlargements tend to develop into actual pathological conditions, is by far the highest in the three groups into which he classifies the cases with enlarged thyroids. Some 38 per cent fall into this group, while of the residual 26 per cent, the adenomas and cystomas together contribute nearly 24 per cent and the colloid goiters the rest. In all three of the groups the incidence for the male is markedly lower than for the female. The incidence curve for age indicates that the number of persons developing goiter increases for both sexes during puberty, and drops to a lower level after the growth of the individual is attained. The curve for the female, however, remains at a high level during the child-bearing period, goes down at about 38 to 40 years and rises again at the meno-

pause. In the male the curve gradually drops till 35 or 40 years when there is a small increase in incidence.

The studies of Marine and Kimball are of immediate practical interest, in that they point the way not only for prevention of this high rate of incidence and its possible pathological sequelae, but also because statistical evidence is given that even when the enlargement is an accomplished fact adequate treatment can be instituted which in a large number of cases results in improvement or cure. These investigators made a study of the pupils in the fifth to the eighth grades of the Cleveland schools and found that goiter may be prevented simply and cheaply in normal individuals merely by the feeding of two grams of sodium iodide daily for a period of two weeks twice yearly. They observed that of 2190 pupils taking this dose, only 5 developed an enlargement of the thyroid, while of 2305 pupils not taking the salt, 495 showed an enlargement of the gland. Moreover, when 1183 pupils who showed a thyroid enlargement at the first examination were treated with the drug, 773 of them presented a decreased enlargement at the second examination, while of 1048 pupils with thyroid enlargement at the first examination who did not take the iodide, but 145 were found to have had a decrease in the size of the gland. The authors go on to state that in the practical application of the treatment there must be kept in mind the three periods when simple thyroid enlargements most commonly occur; fetal life, puberty and pregnancy, and that prevention of goiter in mother and fetus is as simple as it is for adolescence.

Such studies admirably serve to demonstrate the value of the statistical treatment of facts, since they allow the drawing of valid conclusions as to the efficacy of any particular therapy in the treatment of a given actual or potential pathological condition. They are particularly valuable in this case in that they apparently make possible the prevention and treatment of endemic goiter wherever it occurs, providing of course its etiology is the same as for the Great Lakes region.—F. S. H.

REFERENCES

Levin (S.): One thousand one hundred forty-six goiters in one thousand seven hundred eighty-three persons. Arch. Int. Med., Chicago, 1921, **27**, 421-433.

Marine (D.) and Kimball (O. P.): Prevention of simple goiter in man. Arch. Int. Med., Chicago, 1920, **25**, 661-672.

Book Reviews

THE MUTUAL RELATIONS BETWEEN THE ENDOCRINE ORGANS (Die wechselseitigen Beziehungen der Drusen mit inneren Sekretion). Prof. Dr. Erich Leschke. Halle, 1920, Carl Marhold. Verlagsbuchhandlung. 48 p.

This nice, very readable little book gives a good review of our knowledge of the endocrine organs. The author states that nearly all endocrine diseases are polyglanular and that when the origin of a disease may be settled in one organ nearly always the others undergo more or less important changes. It is not right to distinguish between antagonistic and synergistic glands as the question is not so simple. Though no new facts are given, this book will prove useful to medical men, who do not regularly read the literature on endocrinology.—J. K.

Abstract Department

L'ACROMEGALIA. Ferranni (A.), Riforma Med. (Napoli), 1917, 857-861.

The author gives a lengthy discussion on the evolution of the conception of acromegaly, followed by historical information from the work of several pioneers on the subject. After giving the present day recognized symptoms, both physical and histological, the author, like other authorities, comes to the conclusion that the enlargement of the pituitary is associated with the affliction.—D. P.

Contribution to the study of tumors of the ADRENALS (Contributo allo studio dei tumori della ghiandola surrenale). Ausenda (C.), L'Osp. Maggiore (Milano), 1920, **6**, 264-285.

After a detailed discussion of the pathogenesis of hypernephromata the author reviews the benign tumors of the adrenal cortex. He reports having found in adenomata real glandular lumina, while in cortical hypertrophy the lumina were due to degenerative process. Pigmented adenoma is recorded, a few cases of lipomata, while angioma is very seldom found. With regard to the heteroplastic formation of bone tissue the presence of calcification as well as of real bone tissue is stressed. Medullary tumors are reported as paragangliomata, ganglioneuromata and neuroblastomata. The chief discussion concerns malignant tumors and their polymorphism. Six cases are reported of personal observation, detailed histories being given together with the autopsy findings. Chemical analyses of the several tumors failed to yield positive results. The author thinks that the atypical structure of these tumors would explain their functional aberration owing to which the neoplastic element loses its specific function to assume the proliferative (vegetative) one.

The marked polymorphism found in the tumors seems to be a peculiarity of the adrenal blastomata, as the stroma of the parenchyma. As regards the symptomatology in the several cases quoted nothing is recorded, peculiar to the adrenal, save profound asthenia, which could be referred to any other tumor which had progressed to the stages described.—G. V.

(ADRENAL) Recklinghausen's disease with evasive syndrome of adrenal insufficiency (Maladie de Recklinghausen avec syndrome fruste d'insuffisance surrénale). Chauffard (A.) & Brodin (P.), Bull. et mem. Soc. méd. d. Hôp. (Paris), 1920, **44**, 166-169.

Chauffard and Brodin report a case which apparently confirms the connection between Recklinghausen's disease and the suprarenals. Suprarenal treatment was followed by immediate and notable improvement, as in Pic's and Jullien's two cases.—F. S. H.

The ADRENALS in the pathogenesis and treatment of spasms (Die Bedeutung der Nebennieren für die Pathogenese und Therapie des Krampfes). Fischer (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1437-1438.

A theoretical discussion with no report of experimental work. Stimuli producing spasms in animals only produce these spasms when the adrenals are present. When the quantity of adrenal tissue is reduced, the sensibility for spasms is also decreased. When the quantity of adrenal tissue is increased (as after castration or in chronic alcohol intoxication) even small stimuli may produce spasms. When the quantity of adrenal tissue is decreased the irritability of the voluntary muscle is diminished. Not only can spasms be obtained in such animals less easily but also consciousness is no longer lost. In epilepsy the removal of one adrenal will certainly not cure the disease but the spasms will become less intense and less frequent. As we do not know anything about the importance of the adrenals for growth one cannot recommend the operation before growth has finished. The best age is between 20 and 30.—J. K.

(ADRENALS) A note on the effect of irradiation of the SUPRARENAL region in rabbits with Roentgen rays. Grabfield (G. P.) & Squier (T. L.), Arch. Int. Med. (Chicago), 1921, **27**, 168-174.

This study reports the effect of radiating the adrenal region with the "hard type" of x-ray, both through the anterior abdominal wall and from behind. Intact rabbits were used as the experimental animals. The adrenals were examined from 1 to 46 days after the last dose. A few of the animals died, but the majority lived until killed for the purpose of the study. The 3 animals that died all showed a marked increase in the weight of the radiated glands. No reference is made to the use of controls. In general the authors are of the opinion that x-ray treatment of the adrenals induces an increase in their weight.—F. S. H.

Acute ADRENALISM during the course of a secondary syphilis and following a polymorphic erythema (Surrénalité aigue dans le cours d' une syphilis secondaire et à la suite d'un érythème polymorphe). Blum (P.), Bull. et mem. Soc. méd. d. Hôp. d. Par., 1920, 3s., **44**, 1767-1774.

A detailed clinical history presenting no new data.—F. S. H.

ADRENIN glycemia. Bornstein (A.), Biochem. Ztschr. (Berl.), 1921, **114**, 157-164.

The reaction of the respiratory exchange to adrenine administration was determined in several normal and pathological individuals. It was found in general that the drug causes an increase in lung ventilation and consequent decreased alveolar CO_2 tension with its attendant CO_2 expulsion from the lungs: the respiratory quotient rises and an increased carbohydrate oxidation ensues. When the breathing mechanism remains uniform the respiratory quotient sinks to normal or below and a marked hyperglycemia occurs. In this case the adrenine glycemia certainly does not arise from an increased carbohydrate oxidation. Adrenine also brings about a significant rise in oxygen consumptin.—F. S. H.

(ADRENIN) Bronchial asthma: response to pilocarpin and epinephrin. Alexander (H. L.) & Paddock (R.), Arch. Int. Med. (Chicago), 1921, **27**, 184-191.

In this study of 20 cases of bronchial asthma, a general examination with routine laboratory aids and drug tests revealed no constant associated condition. The most frequent finding was an abnormally increased sensitiveness to pilocarpin. These cases frequently presented constitutional defects (status lymphaticus) and abnormal reactions described as characteristic of the condition called vagotonia. The majority of the cases reacted also to the subcutaneous administration of adrenine with an abnormal rise in blood pressure and other characteristic signs—pallor, tremor, sometimes rigor—which are taken to denote an increased sensitiveness to the drug. A relation between low blood pressure and excessive adrenine reaction was apparent, while the smaller number of cases with normal or high blood pressure gave regularly normal reactions. Those cases which were found to react excessively to adrenine were found to be relieved by 0.25 cc.; a much smaller dose of the drug than is usually employed.—F. S. H.

(ADRENIN) Perfusion of the medulla of the turtle. III. Epinephrin. Bush (A. D.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 297-300.

Perfusion of the medulla, which was completely cut off from circulatory connection with the rest of the body but with intact vagus connections, showed no influence on the cardio-inhibitory center. Heinekamp's technique is questioned. (See Endocrin., **4**, 244.)—F. A. H.

(ADRENIN) The point of attack of certain drugs acting on the periphery. I. Action on the bladder. Edmonds (C. W.) & Roth (G. B.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 189-199.

Contraction of the bladder (cat) was obtained from doses of adrenalin, which raised the blood pressure as much as 35 mm. With larger doses such as those which raised the blood pressure 120 mm. relaxation only was produced. "These results were obtained whether the tracings were taken with the abdomen open, the animal being submerged in a warm saline bath, or with the abdomen closed."—F. A. H.

(ADRENIN) The point of attack of certain drugs acting on the periphery. II. Action on the retractor penis muscle of the dog. Edmonds (C. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 201-216.

Adrenine produced contraction in the retractor penis (exact doses not given). After ergotoxin the substance has no effect or gives only relaxation.—F. A. H.

(ADRENIN) III. A note on the action of pilocarpine, atropine and adrenalin upon the tonus of waves in the terrapin heart. Gruber (C. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 23-28.

Adrenine chloride decreased the increased tone set up by pilocarpin but increased the height and rate of contraction. It also antagonized the pilocarpin action in those experiments where only a slowing and decrease of the height of contraction was produced.
—F. A. H.

(ADRENIN) IV. The antagonistic actions of epinephrin and potassium chloride on the tonus waves in the excised terrapin auricles. Gruber (C. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 271-277.

"Epinephin in proper doses causes a disappearance of the general tone and tonus waves aroused by potassium chloride alone or in combination with calcium chloride, causes a reappearance of the contractions if they have disappeared, and increases the rate and the strength of contractions when still present."—F. A. H.

(ADRENIN) The action of epinephrin on the heart. III. The modification of the action of adrenalin by chloroform. Heinekamp (W. J. R.), J. Pharmacol. & Exper. Therap., 1920, **16**, 247-257.

Chloroform produces a toxic or paralytic dilation of the heart, ventricular fibrillation supervening. Because of this action, adrenine is contra-indicated wherever the drug might otherwise be used. The adrenine action is peripheral since it occurs after section of the vagi. The rise in blood pressure by preventing the emptying of the ventricle acts materially in causing the dilatation of the heart.
—F. A. H.

Discharge of ADRENALIN by excitation, of the splanchnic nerve (Décharges d'adrénaline par excitation du nerf splanchnique). Houssay (B. A.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1279-1281.

Adrenalin has been considered a typical hormone because, 1, it is a specific secretion of the chromaffine tissue; 2, it is thrown into the venous blood; 3, it produces definite functional effects. These facts have been disputed, and Houssay undertook to clear up the matter. The experiments were made on dogs, employing the technique of Von Anrep. The (usually) left splanchnic was cut and stimulated with a tetanizing current. The lumbo-capsular veins were dissected free so that they could be clipped or not, as desired. Arterial tension was recorded, and plethysmograms taken of the enervated hind foot. Excitation of the splanchnic with the veins free, is followed by a rise of pressure. This elevation of pressure fails or is attenuated if the veins are clipped. Stimulation of the splanchnic produces direct vaso-constriction and a discharge of adrenalin. Plethysmograms of the denervated foot show contraction of the peripheral vessels.—T. C. B.

Puncture of the bulb and discharge of ADRENALIN (Ponction du bulbe et décharges d'adrénaline). Houssay (B. A.) & Cervera (L.), Compt. rend. Soc. d biol. (Paris), 1920, **83**, 1281.

The spinal cord was sectioned below the twelfth dorsal and in some cases the pneumogastrics were also cut. With the lumbo-capsular veins free, after puncture of the bulb (fourth ventricle) there is a short dilatation of the enervated foot. With the veins clipped there is no constriction of the foot; but if the forceps are removed two or three minutes after puncture of the bulb, the foot is constricted. The experiment shows that puncture of the bulb produces an intense and prolonged discharge of adrenalin.—T. C. B.

(ADRENIN) A comparison of the prophylactic effects of atropin and epinephrin in anaphylactic shock and anaphylactoid phenomena from various colloids and arsphenamine. Hanzlik (P. J.) & Karsner (H. T.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **14**, 425-447.

"When injected together with the antigen or immediately preceding it, epinephrin in the dosage of 0.0005 cc. of 1:10,000 per gram of body weight intravenously, prevents death from true anaphylactic shock in guinea pigs. The partial protection afforded by epinephrin against the symptoms from arsphenamine disturbances is attributed to circulatory improvement. Epinephrin exerts no protection against the effects of agar sol, agar sol-gel, dextrin, peptone (small doses), starch, and when injected after or too long before the antigen in serum sensitized animals."—F. A. H .

Changes in ADRENIN action after excitation of the vagus nerve-endings (Ueber Aenderung der Adrenalinwirkung nach Erragung der vagalen Endapparate). Kolm (R.) & Pick (E. P.), Arch. f. d. ges. Physiol. (Berlin), 1920, **184**, 79-103.

Adrenine doses which have no action on normal hearts (**R. esculenta**) produce either diastolic standstill or negative inotropia and chronotropia in hearts under powerful vagus action through previous treatment with acetylcholine, **pituitrin**, muscarine, or neurine. The standstill, etc., are removed by atropine. The constrictive action on frog-vessels is removed by atropine administration, though after damage to the peripheral ganglia by nicotine it remains unaltered. After perfusion of frog-vessels with dilute acetylcholine solution adrenine is either without action or dilates. A similar reversed action is produced in the alimentary tract. There is a double antagonism between these two compounds. These "vagotropic" actions can be referred to decreased irritability of the sympathetic nerve-endings.—A. T. C.

(ADRENIN) The secretion of bile (Beiträge zur Kenntniss der Gallensekretion. I.). Neubauer (Ernst), Biochem. Ztschr. (Berlin), 1920, **109**, 82-102.

Studies of the amounts, specific gravity, surface tension, viscosity, reducing power and dry matter of bile produced under normal conditions and under the influence of pilocarpin, atropin and adrenin administration in rabbits. Under so-called normal conditions, after the operation, the amount of bile secreted generally slows down during the first hour and a half to a level, which shows periodic variations with a slight tendency to diminution. The specific gravity of this bile is around 1.01 and slowly decreases during the progress of the experiment along with the total solid content, which at the beginning ranges between 2 and 2.5 per cent. The surface tension is quite constant in the different animals, ranging from 617 to 631, and tends to increase during the period of observation. The viscosity lies around 103. Although the urine contains sugar at the end of the experiment, the bile is sugar free. When pilocarpin is injected the course of the bile secretion is as under normal conditions, though possibly to a lesser degree: the specific gravity tends to increase as does the per cent of dry matter, while the surface tension and viscosity are unchanged. No sugar is present in bile after the injection of pilocarpin. Atropin apparently causes no definite change in these factors when injected into rabbits. When adrenin, however, is administered the bile secretion sinks below that obtaining in the control animals; in fact, with large doses secretion is stopped. The specific gravity rises as does the per cent of dry matter. The surface tension falls and the viscosity is often markedly increased. Subcutaneous adrenin injec-

tions always cause the appearance of sugar in the bile; this is rarely seen after intravenous injections.—F. S. H.

On the sensitiveness of the physiological assay of ADRENALIN; constants of action (Sur la sensibilité de l'essai physiologique de l'adrénaline: constantes d'action). Launoy (L.) & Meugny (B.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1510-1511.

In estimating the therapeutic value of adrenalin, two physiological constants are established and defined: a, Toxicity constant, the smallest dose of adrenalin which will cause death in fifteen minutes; b, Cardio-vascular constant—minimum, medium and maximum. The minimum hypertensive dose is the smallest dose that will raise the pressure not less than 1 cm. Hg., nor more than 3 cm. Hg., with return to normal in the second half of the minute following the injection. The medium hypertensive dose is the smallest dose that will cause a rise of pressure not less than 4 cm. nor more than 6 cm. Hg., with return to normal in seventy-five to ninety seconds. The maximum hypertensive dose "approchée" is the smallest quantity of adrenalin that will raise the pressure not less than 7 cm. Hg., and a return to normal in one hundred fifty to one hundred eighty seconds. The toxicity constant 0.00025 to 0.00030 gm. per kilo of body weight.

The cardio-vascular constants are: Minimum, 0.0000005 to 0.000001 gm.; medium, 0.000005 gm. per kilo; maximum, 0.000015 gm. per kilo.

The absolute maximum is 0.00005 gm. per kilo. Its toxicity does not permit a repetition on the same animal.—T. C. B.

(ADRENIN) The part played by the liver in the regulation of blood volume and red corpuscle concentration in acute physiological conditions. Lamson (P. D.), J. Pharmacol. & Exper. Therap., 1920, **16**, 125-134.

The sudden increase in erythrocytes following the intravenous injection of adrenine is caused by an obstruction in the venous outflow from the liver, an increase in the portal pressure and a constant passage of fluid into the liver lymphatics, thus concentrating the blood. It is shown, by removal, that the liver is responsible for this increase.—F. A. H.

(ADRENIN; PITUITRIN) The restoration of the frog's heart in chloroform poisoning. Ransom (F.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **14**, 367-377.

Perfused frogs' hearts depressed by chloroform were restored to normal or nearly normal activity by adding 1:1,000,000 adrenine. Under the influence of adrenine the hearts continued to beat for

some hours in the presence of toxic amounts of chloroform. Pituitrin failed to have any effect as a restorative.—F. A. H.

(ADRENIN) The action of drugs on the output of epinephrin from the adrenals. VI. Atropine; pilocarpine. Stewart (G. N.) & Rogoff (J. M.), J. Pharmacol. & Exper. Therap., 1920, **16**, 71-107.

The adrenal vein blood was collected in a "cava pocket" made by tying the renal arteries and veins, the lumbar veins before they cross the adrenal, the abdominal aorta just above the bifurcation and the tributaries entering the segment of the cava which constitutes the pocket. A cannula was inserted into the lower end of the pocket. Blood was trapped by clipping the cava just below the liver. Epinephrin was assayed on rabbit's intestine and uterus segments. No significant alteration in the rate of output of epinephrin from the adrenals is caused by either of these drugs. A moderate increase may be produced by atropine. In one experiment a moderate depletion of the epinephrin store by pilocarpine was indicated.—F. A. H.

(ADRENIN) Epinephrine content of the suprarenal glands in anaphylaxis. Smith (M. I.) & Ravitz (S.), J. Exper. Med. (Balt.), 1920, **32**, 595-600.

Guinea pigs were used in these experiments, as were rabbits. Although controls were used no note is made of whether or not they were litter controls. The animals were sensitized by a subcutaneous or intraperitoneal injection of ox serum, and after an incubation period of at least two weeks they were reinjected with the antigen intravenously. Immediately after death or at the height of the shock the adrenals were removed, weighed and their adrenine content determined. The results of the experiments were uniformly negative in that the adrenine store of the adrenals was found to remain unaltered under the conditions described.—F. S. H.

(ADRENIN) The blood picture before and after the Goetsch epinephrin test. Trott (Rose M.), Arch. Int. Med. (Chicago), 1920, **26**, 352-356.

Observations were made of 13 cases in which the Goetsch adrenine test was applied. The morphology of the blood was studied. It was found that the subcutaneous administration of from 4 to 8 minims of adrenine will quickly produce a rise in the leucocyte count and cause an absolute lymphocytosis in hyperthyroid individuals. From these experiments it is concluded that in toxic goiter an increase in the lymphocytes is not always present, especially in the borderline cases. A normal differential count is often found and in some cases a polymorphonuclear leucocytosis exists.—F. S. H.

Are the active principles of CORPUS LUTEUM and the PLACENTA specific for the sex (Ist die aus Corpus luteum bzw. Plazenta hergestellte wirksame Substanz geschlechtsspezifisch)? Herrmann (E.) & Stein (M.), Zentralbl. f. Gyn. (Leipzig), 1920, **44**, 1449-1451.

When the active principle of corpus luteum or placenta is injected into female animals the sexual organs become enlarged. In male animals, however, the gonads are reduced in size.—J. K.

Cholelithiasis and involuntary nervous system (Cholelithiasis und vegetatives Nervensystem). Lehmann (G.), Berl. Klin. Wchnschr., 1921, **58**, 30-31.

The author injected pilocarpin, atropin and adrenine into 40 patients with cholelithiasis. He found just the same reactions as in persons without this disease. The antagonism vagotonia-sympathicotonia as described by Eppinger and Hess does not exist. Many patients have vagotonia and sympathicotonia at the same time.—J. K.

Experimental studies on DIABETES. Series I. Production and control of diabetes in the dog. 3. Effect of protein diets. Allen (F. M.), J. Exper Med. (Balt.), 1920, **31**, 555-574, ibid. **4. Control of experimental diabetes by fasting and total dietary restriction.** 574-586, ibid. **5. Various failures of dietetic treatment and their causes.** 587-608, pls. 65-66.

Continuing the studies previously reported (cf. Endocrin., **4**, 446), Allen found that no specific differences were observed between the glycosuric effect of different kinds of protein when fed to his experimental animals. The second paper gives in some detail the effects of dietary restriction on the partially depancreatized dogs, the main point of which was to determine whether downward progress is inevitable in an animal with potentially severe diabetes, so that symptoms must occur ultimately in spite of dietary restriction. The report indicates that there was a gain in tolerance resulting from the treatment. In the third paper the following conclusions are drawn: Practically every detail of clinical diabetes can be produced in partially depancreatized animals. The resemblance is made still more exact by the susceptibility of such dogs to acidosis and coma. The animals at first show considerable tendency to regain assimilation, comparable to that in the early stages of most human cases of diabetes; and in some instances they recover so as to be able to endure any degree or duration of carbohydrate feeding, and can be made diabetic only by further removal of pancreatic tissue. This recuperative tendency can be negatived by overfeeding. With duration of diabetes the power of recuperation diminishes. In the absence of a progressive pancreatitis these dogs

show no downward tendency that is inherent. The conclusions rest upon observations as long as six years from the first pancreas operation and three years of known diabetes. Every detail of the downward progress of human patients on various diets is reproduced in such animals. The important point is that, granting the absence of spontaneous downward tendencies as stated, all the different kinds and degrees of downward progress in the records of animals in this and the preceding paper are purely the results of overstrain of the internal pancreatic function by excess of food. Varying degrees of success and failure in the dietetic control of diabetes are illustrated. The benefit of the classical treatment by exclusion of carbohydrate and limitation of protein is confirmed: though such a result is not permanent.—F. S. H.

A case of hereditary DIABETES. Allen (F. M.) & Mitchell (J. W.), Arch. Int. Med. (Chicago), 1920, **25**, 648-660.

A case report of a patient who came of a family in which 7 out of 14 children of one father (1 by 1 woman, 13 by another) were diabetic. Clinical examination of the patient and his family for general and focal infections, including clinical and serological examinations for syphilis, were negative. In general, the diabetic heredity, which apparently came through the father, was manifest in the children who most resembled him in coloring or complexion, eyes and hair, but the rule was not absolute. As far as the glucose tolerance tests could decide, the diabetic tendency was inherited as a unit character and the tolerance of the remaining children was apparently normal.—F. S. H.

Experimental studies in DIABETES. Series II. The internal pancreatic function in relation to body mass and metabolism. 5. The influence of fever and intoxication. Allen (F. M.), Am. J. Physiol. (Balt.), 1920-21, **54**, 375-381.

The first four papers of this series are published in the American Journal of the Medical Sciences. In the present research it was desired to compare several forms of infectious and non-infectious fevers in their influence on partially depancreatized dogs. Protocols of observations on distemper, pneumcnia, pleurisy, subcutaneous abscesses, infected glands, ratus, peritonitis, etc., are given. The conclusion is reached that the aggravation of diabetes which occurs in human cases in the form of an increased tendency to glycosuria and acidoses does not occur in dogs. Infection and fever have no specific influence in diminishing the diabetic tendency in dogs. The aggravation of human diabetes is a reaction to intoxication rather than to fever.—T. C. B.

Experimental studies in DIABETES. Series II. The internal pancreatic function in relation to body mass and metabolism. 7.

The influence of cold. 8. The influence of extremes of age upon the production of diabetes. 9. The influence of pregnancy upon experimental diabetes. Allen (F. M.), Am. J. Physiol. (Balt.), 1920-21, **54**, 425-459.

These three papers deal with the problems indicated in the subtitles. In the majority of cases cold environment caused hyperglycemia and sometimes glycosuria. These were produced more easily as the diabetes was more severe. In some instances the plasma sugar was unaffected or lowered. "The impression that diabetic patients do worse in cold weather is probably explainable by the discomfort of chilliness when undernourished, the tendency to take more food, and sometimes by the limitations of exercise. These may be important sometimes from a practical standpoint, but any direct influence of climate upon diabetes must be very slight if it exists." "The power to produce glycosuria must be distinguished from the power to produce diabetes."

It is conceivable that senility may influence carbohydrate assimilation by quantitative alterations of metabolism, or functional or anatomic changes in the pancreas. Observations upon senile dogs failed to show any changes from the normal in tolerance, microscopic structure or ratio of pancreas to body weight.

Previous work indicates that glucose tolerance of puppies is less than that of adult dogs. No exact studies of the richness in islands, but no striking departure from the adult average was noticed in the pancreas. The ratio of pancreas weight to body weight was irregular. The general average in puppies did not differ from that in adults. The remnant left after pancreatectomy generally grows considerably in puppies. The tendency to diabetes is distinctly less in puppies.

As pregnancy involves an increased assimilation of food, and the formation of new tissue, it is possible this condition may aggravate diabetes. On the other hand Carlson suggests that diabetes may be prevented by the internal secretion of the fetal pancreas. Partially depancreatized dogs were used, and controls described. The possible effect of changes in the sex organs was studied. No positive influence of the sex glands upon diabetes was demonstrable, and there were no changes in the pancreas with pregnancy or lactation. "Observations on a partially depancreatized dog during pregnancy are opposed to the view that any appreciable quantity of internal pancreatic secretion passes from the fetus to the mother." A distinct lowering of the carbohydrate assimilation was shown during pregnancy. It is suggested that Carlson's results on totally depancreatized dogs are to be interpreted as cachexia. "The slight tendency to aggravation of the diabetes and the ready control by diet support Joslin's experience of the

feasibility of completion of pregnancy by diabetic women under suitable condition of treatment.—T. C. B.

(DIABETES) The relations between glycosuria and glycemia. Faber (K.) & Norgaard, Acta med. Scand. (Stockholm), 1921, **53**, 666-672.

The authors determined the glycemia threshold of 52 diabetics at the cessation of glycosuria following Allen's treatment. In 11 it was found to be 0.09 to 0.13%; in 28 it was 0.14 to 0.18%; in 12 of the remaining 14 the glycosuria was diagnosed as of the alimentary type and gave a glycemia of 0.09 to 0.13%, the remaining two a higher value of 0.16% was found. The glycemia seems to be constant in amount in the same individual for long periods of time, and does not seem to be any different from the normal, particularly in the cases of alimentary glycosuria. There is apparently no connection of the degree of glycemia with the age or sex of the patient or the duration of the disease. A brief discussion is made of the method of testing for the urinary and blood sugar and the time of taking the sample for analysis.—F. S. H.

(DIABETES) On the threshold value for glycosuria. Hagedorn (H. C.), Acta med. Scand. (Stockholm), 1921, **53**, 672-679.

Not of endocrine interest.—F. S. H.

Cases of mild DIABETES. Jacobson (Th. B.), Acta med. Scand. (Stockholm), 1921, **53**, 679-683.

No new data.—F. S. H.

DIABETES The relations between creatinuria and acidosis in—. Lauritzen (M.), Acta med. Scand. (Stockholm), 1921, **53**, 688-700.

Using a method of doubtful exactness for the determination of creatine, the author presents six curves purporting to show the relation between urinary creatine, acetone-bodies and sugar. The results are interpreted as showing that the cause of diabetic creatinuria is like that of acidosis, a deficient metabolism of carbohydrates.—F. S. H.

Pernicious anemia and DIABETIC cases. Slaymaker (S. R.), Med. Rec. (N. Y.), 1916, **38**, 191-194.

The author records symptoms in a case of pernicious anemia and an improved condition due to Fowler's solution and Blaud's pills. To safeguard from remissions splenectomy is contemplated. Three patients exhibiting marked glycosuria together with gangrene or cellulitis were serious cases. An effort is made by diet to reduce the sugar and at the same time avoid acidosis.—F. S. C.

Experimental studies in DIABETES. Series II. The internal PANCREATIC function in relation to body mass and metabolism. 6. Gas bacillus infections in diabetic dogs. Wishart (Mary B.) & Pritchell (Ida W.), Am. J. Physiol. (Balt.), 1920-21, **54**, 382-387.

Four dogs had died of gas bacillus. As gas bacillus is rare in dogs it was decided to follow up these accidental observations by experiments on diabetic dogs, to determine whether the animals are abnormally susceptible to such infection either by reason of excess of circulating sugar, or a lowering of resistance; also if there is an aggravation of diabetes by such infections.

It is concluded from the observations that there is no lowering of resistance in these animals due either to the diabetes or to an excess of sugar. The lowering of tolerance by infection was demonstrable both by feeding and by intravenous glucose tests.

—T. C. B.

DIABETES insipidus. van der Heide (C. C.), Ned. Maandschrift v. Geneesk. (Leiden), 1920, **1**, 618-624.

A report of two cases with normal sella turcica on x-ray examination. In one case **pituitrine** had a temporary good influence, in the other case it was not tried. The article is not of much interest as the patients were not examined in an exhaustive way.

—J. K.

Fat metabolism in DIABETES mellitus. Blau (N. F.) & Nicholson (S. T.), Arch. Int. Med. (Chicago), 1920, **26**, 738-750.

The authors made a study of 26 cases of diabetes with regard to the relation between the blood fat and the blood sugar. The results of the observations lead to a classification of the individuals studied into three groups, on the basis of the effects of the Allen-Joslin method of treatment. About 42 per cent of the cases showed at the beginning of the treatment a marked increase of the blood lipoids accompanied by a drop in the blood sugar. In about 27 per cent of the cases the blood fat seemed to rise and fall with the blood sugar. In about 31 per cent of the cases there was a continued high blood fat content while the blood sugar was decreasing.—F. S. H.

Case of hirsutism with DIABETES mellitus (Un cas d' hirsutisme avec diabète sucré). Emile-Weil (P.) & Plichet, Bull. et mem. Soc. méd. d. hop. de Par., 1921, **45**, 312-320.

A rather complete clinical case report of this condition followed by a detailed autopsy record of a woman of 38 years of age. The hirsutism had appeared at the age of 26 years after a normal pregnancy, and was complicated by obesity and diabetes mellitus, which finally terminated in a galloping febrile tuberculosis. The

only abnormal organ found at autopsy was a fibrous ovary in which no interstitial cells could be found. Since no adrenal changes were found this case must be attributed to the functional and anatomical suppression of the ovary. The author does not think that the simultaneous occurrence of the diabetes and the hirsutism is a coincidence and feels that it is somehow associated with the adrenals, though the connection is hard to see.—F. S. H.

The relation of hypoTHYROIDism to DIABETES MELLITUS. Fitz (R.), Arch. Int. Med. (Chicago), 1921, **27**, 305-314.

A review of the literature and discussion of the earlier findings precedes the report of the findings in 5 cases of diabetes associated with nontoxic thyroid enlargement, in 4 cases associated with toxic thyroid disease, in 3 cases of exophthalmic goiter complicated by diabetes, and 9 cases of exophthalmic goiter and toxic adenoma in which operation was performed. Attention is drawn to certain features that are marked in regard to the results of these studies. It appears that hyperthyroidism and diabetes occur together in the same person in a small number of cases. There is, however, no established evidence that such coincidence is more than chance. The diabetes usually follows the thyroid disturbance, but may precede it, and tends to parallel in severity the severity of the thyroid intoxication. There is no reason for assuming that partial thyroidectomy alone has any curative effect on diabetes, as the patients in this series with nontoxic goiter who were operated on showed no improvement of the diabetes. On the other hand, certain patients with toxic thyroid disease and diabetes, improve to a considerable degree after the thyroid symptoms are checked. This probably occurs because of a change in the rate of metabolism and not because a portion of the thyroid gland has been made functionless.—F. S. H.

DIABETES mellitus, On determination of carbohydrate tolerance in patients with—. Lundsgaard (C.), Acta med. Scand. (Stockholm), 1921, **53**, 685-688.

This article starts off with the statement that no exact definition exists of the expression: individual tolerance for carbohydrate. The author is apparently unfamiliar with the mass of material in the American literature. He goes on to describe results obtained from 40 patients who had been starved till sugar-free and then put on a high carbohydrate diet, increasing every day by 100 calories. His conclusions are too indeterminate to be of wide practical importance.—F. S. H.

DIABETES mellitus. Milber (H. H.), Wisconsin M. J. (Milwaukee), 1918, **17**, 48-51.

A brief discussion of pancreatic diabetes and the Allen treatment. Nothing new offered.—C. W.

The D. N. ratio in DIABETES MELLITUS. Mosenthal (H. O.) & Lewis (D. S.), Johns Hopkins Hosp. Bull. (Balt), 1917, **28**, 187-191.

The authors present the data of one case of diabetes mellitus demonstrating a maximal dextrose-nitrogen ratio of 3.65:1. This maximal ratio has been demonstrated in a few rare cases previously by other observers. Over a period of 12 days this high ratio was shown to exist almost constantly, indicating that the tissues were entirely incapable of utilizing the glucose from either protein or carbohydrates. Calories from fats were partially made use of, but only those from alcohol were entirely metabolized. The islands of Langerhans in the pancreas showed advanced hyaline degeneration. The Allen treatment did not prove efficient in this case, due perhaps to the existence of an infected bunion which complicated the maximal diabetes.—J. M.

The use of a high fat diet in the treatment of DIABETES mellitus. Newburgh (L. H.) & Marsh (P. L.), Arch. Int. Med. (Chicago), 1920, **26**, 647-662.

This paper gives in some detail the various high fat diets used in 10 cases of diabetes mellitus. Three diets are described and tabulated with variations within each group allowing for change of fuel supply. The authors claim that the diets outlined will tend to keep the patients sugar free, will tend to prevent the occurrence of a serious acidosis, will maintain nitrogen balance and will make possible the return to the ordinary activities of everyday life.—F. S. H.

DUCTLESS GLANDS, Studies on the minute innervation of—. White (H. O.), Anat. Rec. (Phila.), 1920, **18**, 265.

Speculative only.—W. J. A.

DWARFISM (Zwergwuchs). Sternberg (K.), Wien, med. Wchnschr., 1919, **69**, 2533.

See Endocrin., **4**, 267.

Combined DYSTROPHY with loss of vesical control. McKendree (C. A.), Neurol. Bull., N. Y., 1918, **1**, 61-63.

A case report not of endocrine interest.—H. W.

(ENDOCRINE ORGANS) A study of unusual endocrine disturbances; their associated myopathies, endocrine balance and metabolism findings. Brock (S.) & Kay (W. E.), Arch. Int. Med. (Chicago), 1921, **27**, 1-37.

An interesting and detailed clinical description and discussion of three unusual cases in which remarkable endocrinopathies are associated with unusual manifestations of the muscular system. The length of the article and the intensive treatment accorded each patient make a satisfactory abstract out of the question, and the article should be consulted in the original by those interested in the phases covered. The first case is one of the dystrophia adiposogenitalis in which it was difficult to differentiate between the hypophyseal and the pure or primary genital forms of the disorder. Although there were no changes in the sella turcica, no signs of intracranial pressure, no polyuria, no subnormal temperature and no blood changes, yet the lowering of the basal metabolism is considered as favoring a pituitary participation as against the **gonadal** determinant. Muscle dystrophy was present. The second case is considered as one in which there was a hyperactive adrenal system because of hirsutism, increased blood pressure, increased muscular strength and cardiac hypertrophy. The definite **thymus** shadow indicates participation of this gland, while the peculiar adiposity, the shallow sella turcica, the increased sugar tolerance bespeak a definite **hypopituitarism.** The increased muscle strength is all out of proportion to the size of the individual. The third case is described as having a cretin facies, a **thyroid** enlargement, a subnormal temperature, an increased sugar tolerance, a thick skin and a hypotonic vegetative nervous system. Testicular atrophy was present. **Parathyroid** involvement is suggested by the myotonia. The three cases studied were examined by almost all of the well known laboratory methods.—F. S. H.

(ENDOCRINE ORGANS) Blood-sugar regulation and the origin of the hyperglycemias. I. Glycogen formation and glycogenolysis. Langfeldt (E.), J. Biol. Chem. (Balt.), 1921, **46,** 381-390.

The first paper in this series deals with a review of the literature and the expression of the views of the author with regard to the mechanism of blood-sugar regulation, as based on the experimental work from the historical point of view. Ibid. II. **Conditions of action of liver diastases.** 391-402. This paper gives the report of the experimental work carried on which leads to the theory developed by the author and which is presented in the 3rd and last part. The experiments consisted in incubating glycogen with liver diastase at different hydrogen-ion concentrations by which the optimum for the reaction was found to be at pH 6,2 in the presence of phosphate ions, and for the chloride diastase at 6,8. When **adrenine** was added to the ferment mixture the reaction optimum is shifted to the alkaline side with the pH of 7,73. When **thyroiodine** is added no change is observed; but when both adrenine and thyroiodine are added a very marked effect is observed in the form of an accelerating action on

glycogenolysis. Extracts of the posterior and anterior lobes of the **hypophysis** have no influence on this process. Ibid. III. **Theory.** 403-409. On the basis of the experimental results and of the exposition of the facts observed by others, an attempt is made to explain the blood-sugar regulation and the mechanism of the origin of the hyperglycemias. In the first place the author is of the opinion that it is not necessary to suppose any cause at a distance serving as a regulating mechanism for liver glycogenolysis and that the theory of the requirement of the organs for sugar may be disregarded. We do not know of nor have we proved the existence of any glycogenolytic agency in the liver other than diastase. As this enzyme action is dependent on the precise regulation of the hydrogen-ion concentration we may suppose that glycogenolysis is regulated by the hydrogen-ion concentration in the liver tissue. According to this opinion sugar formation should be constant. Under normal conditions the liver always discharges the same quantity of glucose, i. e., with a constant blood flow and at a constant temperature. A part of the glucose is burned, a part is stored in the muscles and tissues as glycogen, and the remainder returns to the liver and is reformed into glycogen. Here glycogen formation depends upon the **pancreas** hormone, and the material for this formation is chiefly the carbohydrates and the proteins of the food. This theory also explains why the blood-sugar concentration is constant when the liver is exhausted of glycogen, and in starvation. The conclusion is reached that glycogen formation and glycogenolysis are consecutive processes. Now hyperglycemia may arise in three ways. By a change in the hydrogen-ion concentration of the liver tissue, by a displacement of the curve of action of the liver diastase such as may be produced by adrenine or by adrenine and thyroiodine combined, and by a lack of formation of glycogen on account of the insufficient functioning of the pancreas hormone.—F. S. H.

A note on the brown granules formed in some ENDOCRINE ORGANS. Lim (R. K. S.), J. Physiol. (Lond.), 1920, **54**, xxx.

"These granules have been noticed in the **suprarenal** cortex of the cat, the **corpus luteum** of the rabbit, and the pars nervosum of the human **hypophysis.**" Their staining properties are described. —T. C. B.

The process of growth during hypofunction of one or more ENDOCRINE ORGANS, induced experimentally in young cats and dogs (Le processus de la croissance dans l'hypofunction d'une ou plusieurs glandes endocrines, provoquée expérimentalement chez les chats et les chiens tout jeunes). Pugliese (A.), Arch. ital. de Biol. (Torino), 1920, **70**, 1-34.

The simultaneous extirpation of one **adrenal** and one **thyroid** lobe with or without splenectomy produces no apparent effect in adult or nearly adult cats and dogs. They remain in good condition, can procreate and raise offspring. Unilateral **thyro-parathyroidectomy** favors increase of body-weight in very young animals; removal of one adrenal slows it. Kittens below the age of 4 months do not as a rule survive the removal of one adrenal and one thyroid lobe. After an initial lowering of body-weight following the operation, succeeds a period of feeble and difficult development, at the end of which the body-weight is about one-fifth more than that preceding operation. The succeeding decline is more or less rapid, the animals dying between 80 and 104 days after the operation. Body fat is greatly reduced. The bones are smaller, thinner, contain much less nitrogenous material and fat, while their ash, calcium, and phosphorus content are increased. At death the remaining adrenal and thyroid lobe, and the **pituitary** appear to be hypertrophied. Splenectomy has no effect on these results. The effects on pups are less. They survive the operation, grow at a slower rate than the controls, fatigue more easily, present less resistance to disease, but the body temperature remains unaltered, and though the bones are smaller and thinner, their composition is not greatly altered. Fat is somewhat diminished, both in bones, blood, and liver, and the fat depôts are diminished. The remaining adrenals of these animals do not appear to hypertrophy, the thyroid may or may not do so. To a hypertrophied thyroid corresponds a reduced **thymus**; to a thyroid appearing normal corresponds a thymus greatly enlarged. The pituitary is only one-fourth to one-fifth of normal size. Of the other organs only the liver and heart show decreases greater in proportion than that of body-weight.—A. T. C.

(GENERAL) Review of symptoms of osteomalacia as a pluriglandular endocrine disorder (Uebersicht über die Symptomatik der Osteomalazie als innersekretorischer pluriglandulärer Erkrankung. Nach 11 eigenen und nach Literaturbeobachtungen). Naegeli (O.), München med. Wchnschr., 1918, **65**, 585-586.

A general consideration of the pathology of the muscular, skeletal, nervous and endocrine system as associated with osteomalacia. Osteomalacia may be looked upon as the result of an unbalanced endocrine system.—C. W.

(GENERAL) Beta-imidazolylethylamine as a powerful stimulant of the gastric glands (Beta-imidazolyläthylamin als mächtiger Erreger der Magendrüsen). Popielski (L.), Arch. f. d. ges. Physiol. (Berlin), 1920, **178**, 214-236.

Histamine has been shown to be produced by the action of bacteria on histidine. Injected intravenously into dogs it rapidly pro-

duces a fall of blood pressure, with excitement, then depression, secretion of saliva, tears, and pancreatic juice, urination and defaecation. Introduced into the intestine it is without action. Injected subcutaneously, it only induces acid gastric secretion. Injection of 0.00021 gm. per kilo body-weight produces 3.75 cc. per kilo. This secretion takes place after section of the vagi and injection of atropine, and is probably directly on the cells. This substance is probably produced when tissue extracts are subcutaneously injected.
—A. T. C.

(GENERAL) Influence of acids on the stimulative action of tissue extracts on gastric secretion. (Einflus der Saüren auf die Magensaftsekretion erregende Wirkung der Organextrakte). Popielski (L.), Arch. f. d. ges. Physiol. (Berlin), 1920, **178,** 237-259.

Tissue extracts introduced subcutaneously induce, like histamine, marked gastric secretion; acids such as citric, acetic, mono- and di-chloracetic, lessen the action. Trichloracetic acid increases it. The active substance (probably histamine) probably unites with the first series of acids. Giddiness and apathy, which follow subcutaneous injections of histamine, result from the abstraction of fluid from nerve cells consequent on the marked gastric secretion. Therapeutically this substance should not be used intravenously, since it can lead to dangerous results.—A. T. C.

(GONADS) Hermaphroditism in China. (Author's name omitted.) China M. J. (Shanghai), 1920, **34,** 608-611.

A useful review of literature, special attention being devoted to an article by Berthold Laufer entitled "Sex Transformation and Hermaphrodites in China" (A. J. Phys. Anthrop., 1920, iii, 259-262). One case of pseudo-hermaphroditism is reported.—E. V. C.

(GONADS) Hermaphroditism in fundulus heteroclitus. Chidister (F. E.), Anat. Rec. (Phila.), 1917, **12,** 389-396.

The author describes the only known case of hermaphroditism in this species. The discovery is of particular importance because this species is much used in experimental embryology. It was a conspicuously well marked male in external appearance. The gonads which gave the secondary sex characters were entirely male and were in no way attached to the diffuse egg masses. The latter were found in close association with the organs of digestion and in some cases occupied positions under the serous coats of the organs. Apparently well developed eggs were present and were found to be incapable of fertilization. The testes were entirely normal. The striking feature was that the diffuse egg masses exerted no influence on the secondary sex characters as do normal condensed ovaries.—J. M.

(GONADS) A case of Chinese hermaphrodite and a case of a dicephalous monster. Lin (C. S.), Nat. M. J. China (Shanghai), 1920, **6**, 208-211.

A description of one case of pseudo-hermaphroditism.—E. V. C.

(GONADS) True hermaphroditism in man (Ueber wahre Zwitterbildung beim Menschen). Polano (O.), Ztschr. f. geburtsh. u. gynäk. (Stuttgart), 1920, **83**, 114-150.

This is an extended report of a case of true hermaphroditism in an individual of 24 years of age in whom there were present the external and internal genitalia of both sexes. The **ovaries** gave every evidence of functional activity, though the **testicles** were not yet at the adult stage. The male and female hormonal activities due to the gonads were apparently in full operation.—F. S. H.

(GONADS) The metabolism of the eunuch. Read (B. E.), J. Biol. Chem. (Balt.), 1921, **46**, 281-283.

Report of the amounts of total nitrogen, urea, ammonia, creatinine and creatine in the 24 hour urine of a eunuch. Creatine was found to be present in some quantity as well as was ammonia. The abnormal creatine content in castrated males was confirmed in 5 other cases. There appear to be differences in the effect on metabolism that are related to the different ages at which the individuals are castrated. From the fact that creatine is found in the urine of these individuals the conclusion is made that the removal of the male organs at a suitable age tends to develop chemical as well as secondary sexual female characteristics in the individual.—F. S. H.

(GONADS) Atypical male sex-ensemble in the domestic goat. Stone (Robert S.), China M. J. (Shanghai), 1920, **34**, 611-623.

The author's abstract is as follows: "A case of atypical male sex-ensemble occurring in a goat is reported. The abnormality consisted essentially of persistence and growth in this male individual of certain of the female genital ducts and of inhibition of development of the male external genitalia. The abnormality was seen to be the result of unusual embryological development. The cause probably depended upon some temporary derangement of the endocrine system during embryonic life, which gave rise to a physiological state favoring the development of female characters."—E. V. C.

(GONADS) Ovulation, corpus luteum and menstruation (Ueber Ovulation, Corpus luteum und Menstruation). Tschirdewahn (F.), Ztschr. f. geburtsh. u. gynäk. (Stuttgart), 1920, **83**, 80-111.

This is another of those lengthy papers on the factors of the menstrual cycle, in which all the previous studies are reviewed.

Extensive tables are given of the type and time of menstruation in various patients, but no statistical study is attempted. The opinion is expressed that one, rarely two, follicles periodically ripen in the healthy woman. The follicles rupture individually and in the same person between the 10th and the 26th day after menstruation. While the ovum is passing through the tube the transformation of the follicle to luteum is taking place. The hormone formed by this, which perhaps is already performed by the theca lutein cells, acts on the uterine nucosa to prepare it for implantation or menstruation.

—F. S. H.

Epilepsy and HYPOPHYSEAL adiposity (Epilepsie combiniert mit endogener [hypophysärer] Fettschut). Ibrahim, Kor. Bl. d. allg. ärztl. Ver. v. Thüringen (Jena), 1919, **48**, 119.

See Endocrin., **4**, 128.

Tumor of HYPOPHYSIS (Hypophysisgezwel). Klinkert (H.), Ned. Tijdschr. v. Geneesk (Haarlem), 1921, **65**, 466-467.

The patient reported in this study was 40 years old. His illness began with atrophy of both optic nerves and hemianopsia. No headache was present. The pressure of the cerebrospinal fluid was found increased by the lumbar puncture test. In the cerebro spinal fluid albumin was found. The x-ray showed changes in the sella turcica. No symptoms of acromegaly were present.—J. K.

(HYPOPHYSIS) Adiposo-genital dystrophy accompanied by epileptic attacks (Distrofia adiposo-genital frusta con ataques epilepticos). Malamud (T.), Prensa med. Argent. (Buenos Aires), 1920, **7**, No. 3, June 30th.

Case report of an epileptic of 14 years with adiposity and menstrual difficulties. Improvement by subcutaneous hypophyseal opotherapy.—B. A. H.

(HYPOPHYSIS) Cure of dystrophia adiposo-genitalis on basis of hereditary lues (Heilung von Dystrophia adiposogenitalis auf der Basis von Lues hereditaria). Nonne (M.), Deutsche med. Wchnschr. (Leipz. u. Berl.), 1918, **44**, 536.

A report of a case of adiposo-genitalis showing adiposity, infantile genitals, absence of secondary sexual characters, polyuria and infantile psyche. The patient gave a three plus Wasserman reaction. The mother and three of her sisters also gave positive Wasserman reactions and demonstrated signs of hypophyseal disturbances.—C. W.

Muscular INFANTILISM. Gibson (A.), Arch. Int. Med. (Chicago), 1921, **27**, 339-350.

This is a case report of a patient complaining of muscular weakness. There was a creatine excretion which suggested infantilism, a marked adiposity, a normal blood sugar and a normal sugar utilization. **Adrenine, pituitrine,** and **thyroid** substance were administered at one time or another and the metabolism was studied in the two latter attempts at medication. Pituitary administration had no effect, while during the thyroid administration excessive carbohydrate was used without obviously modifying the thyroid effect. There was initially a slight increase in creatine, which lasted two or three weeks, which later was not obtained. The diagnosis is tentatively given as muscular infantilism.—F. S. H.

(INTERNAL SECRETIONS) Tissue extracts with specific action (Studien über die von einzelnen Organen hervorgebrachten Stoffen mit spezifischer Wirkung. III.). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berlin), 1920, **182,** 28-49.

The "optones" (completely hydrolysed products) of the **corpus luteum** and **testes** produce a mydriatic action on the enucleated frog's eye, and diastolic standstill on Straub's heart-preparation, and seem to belong to the group of parasympathetic inhibitory substances. Pituitary and thyroid optones produce miosis, and either no heart action or a powerful pulse increase. The **thymus** optone produces mydriasis, but only slight pulse slowing. The **ovarian** and **anterior pituitary** optones promote **adrenin** mydriasis. When miotic and mydriatic optones are used together, mydriasis is usually pronounced. Only a **thyroid-testis** optone combination leads to miosis.
—A. T. C.

The INTERNAL SECRETIONS. Friedman (E. D.), New York, 1919, Wm. Wood & Co., 36 p., 8°.

See Endocrin., **4,** 470.

The influence of glands with INTERNAL SECRETIONS on the respiratory exchange. 1. The effect of the subcutaneous injection of adrenalin on normal and thyroidectomized rabbits. Marine (D.) & Lenhart (C. H.), Am. J. Physiol. (Balt.), 1920-21, **54,** 248-260.

Asher and Flack gave the first concrete evidence that there was a relation between **thyroid** and **adrenals.** They showed that stimulation of the laryngeal nerves in rabbits prolongs the rise of blood pressure following injections of adrenalin. The authors have compared the effect of subcutaneous injections of adrenalin in normal and thyroidectomized rabbits. The dose of adrenalin was arbitrarily fixed at 0.5 cc. per kilo. The rabbits were deprived of food for 15 hours before the experiment. The results on rabbits confirm those of Sandiford on man. Adrenalin causes a rise in oxygen con-

sumption in both normal and thyroidectomized rabbits. The O_2 consumption following adrenalin is delayed in thyroidectomized rabbits, and does not last so long. The decrease in the metabolic rate following thyroidectomy is gradual, and requires several days for its demonstration.—T. C. B.

LYMPHATISM with disturbed INTERNAL SECRETIONS (Lymphatismus mit innersekretorischen Störnngen). Moose (M.), Berl. klin. Wchnschr., 1920, **57**, 971-974.

In a girl of 19, 5 weeks after an attack of influenza, there developed a general weakness with rheumatic pains, local edema of face and legs, dryness of skin, enlarged **thyroid,** large tonsils and enlarged follicles of the tongue. A persistent **thymus** could be detected by percussion. Tuberculosis of both lungs was present.—J. K.

(INTERNAL SECRETIONS) Experimental studies of the properties of surviving vessels tested by chemical methods of stimulation (Experimentelle Studien über die Eigenschaften überlebender Gefässe unter Anwendung der chemischen Reizmethode). Rothlin (E.), Biochem. Z. (Berl.), 1920, **111**, 219-256.

This first paper is mainly concerned with a description of the conditions regulating the proper conduction of experiments for the study of vaso-active compounds on isolated blood-vessels, which leads to the conclusion that such material is quite suitable for qualitative work where high sensitivity is required. II. The action of some chemical vaso-tonic substances of organic nature (II). Experimentelle Untersuchungen über der Wirkungsweise einigen chemischer, vasotonisierender Substanzen organischer Natur auf überlebende Gefässe), idem. 257-98. Using the isolated blood-vessel as the test organ R. was unable to demonstrate the presence in norm. blood of any vaso-tonic substance besides **adrenin** with any safe regularity, although in blood serum there is found a vaso-constrictor substance which is not adrenin. Adrenin action is then tried out on various blood-vessels from different organs and different animals. The irritability of the renal vessels towards adrenin is the same as is that of the others studied: they can be constricted or dilated at will by the drug, depending on the dose employed, and both the proximal and the distal portions react in the same way. However, on the coronary vessels a qualitative and quantitative difference is obtained. The coronary vessels from the equine type are contracted. In the bovine type weak concentrations cause a weak contraction, while stronger doses, after a latent period, bring about a dilation. The vessels from swine and sheep act similarly. On the isolated lung vessels of both equine and bovine type adrenin in normal doses produces contraction. III. idem. 299-335. This third and last paper of the series first takes up the effect of Beta-imidazolylethylamine

in the same manner **adrenin** was studied. Apparently there exists a qualitative difference in the action of histamine on different surviving blood-vessels. Arterial strips from various sources from various kinds of animals, as well as the vessels of the rabbit ear, are regularly contracted by the compound in concentrations in which adrenin has a similar action. All the vessels of the frog, however, are inconstant in their response and the effective doses are from 10 to 100 times as weak. **Pituglandol** is also inconstant in the type of its reaction on the frog, though it constricts the vessels of the rabbit ear. **Lienin,** a preparation from the **spleen,** acts as a vaso-constrictor on the isolated segment, the vessels of the rabbit ear and those of the frog's vessels that are capable of being so influenced. These effects on the isolated blood-vessel strips are in general quite comparable with those obtained **in vivo,** and serve to demonstrate that the latter are largely the results of the response of the tissue itself and not due to mediation through extraneous sources.—F. S. H.

The effect of MENSTRUATION and OVARIOTOMY on the cutaneous reaction to tuberculin (La cuti-réaction a la tuberculine pendant les règles et après ovariotomie). Coulaud (E.), Bull. et mem. Soc. Méd. d. hop. de Par., 1921, **45,** 155-159.

C. observed that the skin-test with tuberclin was negative in 2 cases during the first day of menstruation, becoming positive 8 days later. In a third case the reaction was negative on the day the periods were expected but did not appear, and was positive 15 days later, although menstruation had not occurred. In 2 out of 5 goitrous cases the reaction was very weak on the first 2 or 3 days of the periods and later became strongly positive. Tests were also made on 60 apyretic tubercular patients—and it was noticed that the reaction is weaker at the beginning of the menstrual period. This was very marked in 12 of the cases and was substantiated by suitable dilution tests. When patients were tested after ovariotomie some 44% of the unilateral operated gave negative reaction, while over 50% of the bilateral cases were negative. Since this diminution of sensitivity to tuberculin is apparently coterminous with a diminution in immunity, the author goes on to discuss in general terms the part possibly played by the **thyroid,** the **ovaries** and the other endocrine glands in the reaction of the organism to the tuberculin skin-test.

—F. S. H.

MENSTRUAL blood (Das Menstrualblut). Stickel (M.) & Zondek (B.), Ztschr. f. Geburtsch. u. gynäk. (Stuttgart), 1920, **83,** 1-26.

The authors have undertaken an intensive study of the properties of menstrual blood, the results of which are serviceable in differentiating this excretion from possible pathological conditions. They hold that for an accurate examination to be made the blood

must be collected from the uterine cavity since the passage through the cervix produces certain morphological changes. In addition the sample to be examined must be thoroughly shaken before study. No changes can be detected in the hemoglobin content and morphological blood-picture of whole blood during menstruation. In menstrual blood an oligocythemia is present, the erythrocytes range between 2,600,000 and 3,270,000. Leucopenia is also evident. The hemoglobin of menstrual blood is always less than that of whole blood, but the diminution is not proportional to the decrease in erythrocytes. On account of this fact the hemoglobin content is relatively too high and is usually over 1. This phenomena is attributed to a local partial hemolysis. The lymphocytes tend to increase at the expense of the neutrophils. The specific gravity of menstrual blood is relatively low, the water content is high and the coagulation property is lost.—F. S. H.

Formation of the definitive cortical layer and origin of definitive ova in the OVARY of the cat (Formation de la couch corticale définitive et origine des oeufs définitives dans l'ovaire de chatte). De Winiwater (H.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1403-1405.

Histological matter only—T. C. B.

Definitive cortical layer at the hilus of the OVARY and pseudo-néoformation (Couche corticale définitive au hile de l'ovarie et pseudo-néoformation ovulaire). De Winiwater (H.), Compt, rend. Soc. de biol. (Paris), 1920, **83**, 1406-1408.

Histological matter only—T. C. B.

Autotransplantation of the OVARY in the omentum (Autotransplantation von Ovarien uns Netz). Köhler, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 91.

In serious disease of the adnexae in young women the author implants some slices of ovary into the omentum. The slices must be thick to prevent resorption. In 5 of the 6 cases the effect was good and no symptoms of castration were seen. In one case menstruation reappeared regularly.—J. K.

(OVARY, TESTIS) An analysis of the behavior of organs after transplantation in the rat; and of the power of resistance of the constituents of the various organs. Loeb (L.), J. Med. Research (Boston), 1918, **39**, 189-216.

Experiments are reported in which various tissues were transplanted from one rat to another or to itself. The factor governing their growth or failure to grow under various conditions are studied in considerable detail. Among the tissues so studied were the ovaries

and testes. It was found in the case of the ovaries that the Graffian follicles matured and from them normal corpora leutea developed whether the ovaries were transplanted to the male or into another female. A corpus luteum existing in the ovary at the time of transplantation, however, was found to undergo rapid degeneration. In the case of testicle transplantation it was found that the interstitial tissue perishes while the elements of the tubules soon degenerate.
—J. M.

(OVARY) Circumscribed edemas. Diseases of the lymphatic system. Pathogeny and treatment (Les oèdemes circonscrits, maladies du système lymphatique, pathogénie et traitement). Mauriac (P.), Ann. Méd. (Paris), 1920, **8**, 271-279.

This paper contains a brief review of the general subject of circumscribed edemas and takes up in particular a case of a woman 48 years old complaining of localized edema of the hands and digits. **Thyroid** treatment was inefficacious. A turpentine injection produced favorable results, subsidence of the edema and return of the menses which had been lacking for 10 years. The cause of the disturbance is attributed to a relative ovarian insufficiency.—F. S. H.

The tendency of carcinoma of the PANCREAS to spread by blood-vascular invasion. Adams (F. D.), Arch. Int. Med. (Chicago), 1921, **27**, 175-183.

In the group of cases here reported, the carcinoma of the pancreas showed a definite tendency to invade the local blood vessels and to disseminate metastases to the liver and lungs, and in some instances to other parts of the body. The type of tumor in which this occurs is the adeno-carcinoma.—F. S. H.

(PANCREAS) Experimental studies in diabetes: Series II. The internal pancreatic function in relation to body mass and metabolism. Allen (F. M.), Am. J. M. Sc. (Phila.), 1920, **160**, 781-801.

Removal of as little as a fourth or a third of the pancreas causes dogs to show an increased tendency to glycosuria. Successive removal of portions of the pancreas shows that the point at which diabetes begins is sharp and definite. Removal of about seven-eighths of the gland is necessary to produce diabetes in the dog. Since a relatively small mass of normal tissue can prevent diabetes, it is suggested that any positive means of augmenting the endocrine pancreatic function even by a little would give therapeutic results far surpassing those of the negative plan of sparing the function by diet.—W. J. A.

(PANCREAS) The concomitance between the appearance of the functional islands of Langerhans in the embryo and the establish-

ment of the glycogenic function of the liver (De la concomitance entre l'apparition des îlots de Langerhans fonctionnels chez l'embryon et l'établissement de la fonction glycogénique du foie). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1448-1450.

A histological study. The conclusion is reached that the glycogenic function of the liver is established at the time when the islands of Langerhans change from the embryonic to the functional type.—T. C. B.

On the development of the functional islands of Langerhans in the embryonic PANCREAS (Sur le développement des îlots de Langerhans fonctionnels dans le pancréas embryonnaire). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1921, **83**, 1445-1448.

Histological material only.—T. C. B.

(PANCREAS: SUPRARENALS) Relation between the pancreas and the suprarenal capsules, from the point of view of diabetes (Relation entre le pancréas et les capsules surrénales ou point de vue du diabétes). Hedon (E.) & Giraud (G.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1310-1312.

In a preceding note (C. R. Soc. de Biol., 1920, **83**, 330) the authors have given the curve of glycemia during the first hours following pancreatectomy. In this paper they discuss the question whether there exists a functional relation between pancreas and suprarenals in relation to the metabolism of sugar. The experiments were made on dogs. Pancreatectomy associated with extirpation of the capsules gave rise after some hours to hypoglycemia. In one dog the removal of a pancreatic graft and the left suprarenal (the pancreas and right suprarenal had been previously removed) was followed by hypoglycemia. In order to eliminate the possibility of surgical shock causing the effect, the glands were crushed below the suprarenal veins and the inferior poles resected. Immediately after, total pancreatectomy, the blood-sugar fell during the first fifteen minutes and then rose markedly. Another dog survived 12 days with an intense diabetes. The conclusion is that the result of extirpation of the pancreas with total capsulectomy cannot be attributed simply to traumatism. The effect of capsulectomy on a dog previously depancreatized and in full diabetes is negative for 24 hours. The amount of blood-sugar then begins to fall. The experiments are favorable to the hypothesis of a functional relation between the pancreas and suprarenals, but the problem is still obscure.
—T. C. B.

(PANCREAS) Giant islands of Langerhans in a new-born child of a glycosuric mother (Ilots de Langerhans géants chez un nouveau-né,

issu de mère glycosurique). Dubreuil (G.) & Auderodias, Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1490-1493.

A history of a case of glycosuria in a pregnant woman in whom delivery was induced at the beginning of the ninth month. The child weighed 5050 gm. and lived but a few minutes. Examination of the foetal pancreas showed the islands of Langerhans to be enormously increased in size, appearing as large masses of compact epithelium. As the blood of the mother contained a large amount of sugar the fetal blood must have been hyperglycemic by reason of the placental exchange. The excess of nutritive material accounts for the exaggerated weight of the fetus. But the fetus was required to continually destroy this excess of sugar in the blood and consequently the pancreas had developed the islands of Langerhans to meet the emergency. The authors think this is positive experimental proof of the function of the islands in the regulation of the blood sugar. In the presence of exaggerated need, the organ hypertrophies.—T. C. B.

(PANCREAS) A research on blood-sugar in depancreatized dogs. Delatour (B. J.), Arch. Int. Med. (Chicago), 1920, **25**, 105-110.

The effect of the administration of adrenin on the blood-sugar of completely depancreatized dogs was studied some days after the operation. It was found that the complete removal of the pancreas produced a permanent hyperglycemia which was but little if any increased by the intravenous injection of epinephrin. The author is of the opinion that in such animals the sugar is passing freely into the blood unburnt and that, therefore, adrenin can have very little further effect in inhibiting sugar metabolism. He concludes that it is reasonable to believe that the pancreas produces some substance which favors the metabolism of sugar in the tissues since sugar injected intravenously is not handled as readily in the depancreatized dog as in the normal animal.—F. S. H.

The rôle of the PANCREAS in hyperglycemia from ether. Ross (E. L.) & Davis (L. H.), Am. J. Physiol. (Balt.), 1920, **54**, 391-397.

There has been a tendency to forget the pancreas when dealing with glycosurias and hyperglycemias not directly associated with diabetes. In the present paper the hyperglycemia induced by ether was investigated. Dogs were used. One group was partially depancreatized, and another group completely depancreatized. The effect of ether anesthesia on the urine dextrose was measured. In both groups the hyperglycemia induced by ether was practically the same as that of normal dogs. There is a marked decrease in the dextrose output in the half hour urine during anesthesia, compared

with that of a half hour before anesthesia. Ether markedly decreases the rate of mobilization of dextrose. The results lead to the conclusion that in normal animals ether causes hyperglycemia by reducing the influence of the pancreatic secretion on glycolysis. —T. C. B.

Carcinoma of the PANCREAS. Speed (K.), Am. J. M. Sc. (Phila.), 1920, **160**, 1-10.

Not of immediate interest.—W. J. A.

The PARATHYROID bodies and Bright's disease. Bergstrand (H.), Acta med. Scand. (Stockholm), 1921, **53**, 644-651.

The author found that in ten cases out of fifty where the parathyroids showed pathological conditions there was an accompanying marked renal disorder. This finding, taken together with the fact that the literature also reveals the occasional concurrence of parathyroid and renal disorders, leads Bergstrand to the opinion of a possible correlative pathogeny. He states that the rabbit is the best animal for use in such studies because it is the only animal in which the measures of the weight of the endocrine glands is established. Apparently he is ignorant of the work of Donaldson and Hatai on the albino rat.—F. S. H.

(PARATHYROIDS) Observations on parathyroidectomized dogs. Hastings (A. B.) & Murray, Jr. (H. A.), J. Biol. Chem. (Balt.), 1921, **46**, 233-255.

The study reported in this paper was limited to an investigation of the blood-serum calcium, the alkaline reserve of the blood plasma, the hydrogen-ion concentration of the blood plasma, the blood-sugar and the symptomatology of parathyroidectomized dogs. It was found that the hydrogen-ion concentration of the plasma remained within normal limits, though the carbon dioxide combining capacity of the blood was slightly diminished. The calcium content of the serum was cut in half within a few days and was hardly diminished subsequently. When the concentration reached approximately 7 mg., tetany developed. Phosphorus and sulfur were increased in the blood. No significant changes were found in the blood-sugar. Hence the previously observed calcium deficiency in parathyroidectomized dogs is verified, but no support is found for the theories based on a disturbed acid-base equilibrium.—F. S. H.

Mammalian morphology of the PINEAL (Bidrag Til Kundskaben om Corpus Pineale). Krabbe (K. H.), Det. Kgl. Danske Videnskabernes Selskab., Biol. Meddelelser (Copenhagen), 1920, II, 2.

This is a monograph dealing with the morphology of the pineal body in mammals. The author reviews the literature and reports

his own findings of the embryology, anatomy, and histology of the following classes of mammals: Monotremata, Marsupialia, Insectivora, Chiroptera, Rodentia, Proboscidea, Ungulata, Sirenia, Edentata, Carnivora, Pinnipedia, Cetacea, Primates. The conclusions are that great variation occurs within the different species of mammals, yet the glands have certain characteristics which are common to all, viz., the organ is cellular and there is no division into a cortical and medullary portion. The parenchyma consists of pineal cells, nervous elements, and neuroglia. The pineal cells form the main bulk of the organ. These have a bullet-shaped nucleus containing one to two nucleoli. In man and some of the higher mammals there sometimes occur cells having irregular nuclei. Numerous mitotic figures are present in these classes. Nuclear excretions may be seen. The cytoplasm of the cells is scant and cellular processes are absent. Such cells are distinctly different from any other cells found in the nervous system. They may be related to neuroglia. The nerve fibers and neuroglia form a network around the pineal cells. Nerve elements, in the form of nerve cells and fibers, are not conspicuous in the pineal body except in man and some of the higher monkeys. The amount of neuroglia present differs greatly in different species. The blood supply was abundant in all the glands examined. Pigment was also present in all the mammals examined, especially marked in horses. Concretions were found in glands from man, ox, and chimpanzee.

Embryologically the pineal body develops from an outgrowth of the roof of the diencephalon. The organ is not a rudimentary type, nor is there any reduction of it at puberty. The organ may not have the same function in all mammals; however, the structure suggests a glandular function. It may also serve as an outlet for the spinal fluid.—D. J. G.

Effect of feeding the PINEAL body upon the development of the albino rat. Sisson (W. R.) & Finney (J. M. T. Jr.), J. Exper. Med. (Balt.), 1920, **31**, 335-346, 1pl.

The method employed in the experiments was to feed desiccated pineal body to rats and compare the resultant growth as measured by weight changes with controls from the same litter. Observations were also made of the changes in the appearance and texture of the coat, descent of the testes, state of nutrition, skeletal changes and activities. At autopsy measurements were made of the body and tail lengths and tissue was obtained from the endocrine organs and studied histologically. It is the opinion of the reviewer that this is a most carefully carried out series of experiments. During the entire series of experiments the animals all remained in an excellent state of nutrition. Although the pineal powder was given in large doses, it in no way affected their general health. The

activities of the test animals equalled and corresponded to those of the controls. In no instance was any sexual precocity noted. The testes of both the test and the controls descended almost simultaneously; furthermore, no differences were noted in the appearance, size, or consistency of the testes of the test and control animals of the same litters. There was essentially no variation between the weight of the pineal-fed animals and their controls, either during the course of the period of study or at its termination. Microscopic studies of the endocrine organs of both control and pineal-fed rats revealed normal conditions. As far as these observations go, then, they present no evidence of the presence of an active substance in the pineal body that influences growth of the characters studied.—F. S. H.

On the presence of histamine in extracts of the posterior lobe of the PITUITARY gland and on preliminary experiments with the pressor constituent. Abel (J. J.) & Nagayama (T.). J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 347-399.

Extracts made from fresh pituitary glands in which long boiling and long exposure to acids is avoided, contain a small amount of histamine.

Extracts which are employed in therapeutics contain more of this amine. It was estimated from one experiment that a 1 c.c. phial of such a preparation contained about 0.025 mgm. of histamine. The method of preparation determines to some extent the amount of histamine present. Continued boiling of a fresh extract of the pituitary with dilute acid increased the amount of free histamine and abolished the pressor substance. Extracts treated in this way produce a marked fall in blood pressure which is due to histamine and a histamine-like substance, about four-fifths of the effect being due to the latter. The latter substance gives the Pauly reaction but not the biuret reaction, is soluble in alcohol but insoluble in chloroform. There is a residual oxytocic activity after the treatment of pituitary extract with acid, this being due to histamine and the histamine-like substance.

Histamine and the histamine-like substance are apparently not specific constituents of the infundibulum as they occur in animal extracts of all kinds, being formed from the hydrolysis of proteoses. The observations of these authors point to the conclusion that there is but one hormone in the infundibulum.—F. A. H.

A pressor compound from the PITUITARY gland. Crawford (A. C.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 81-94.

Extraction by absolute ethyl alcohol was used to remove the depressor substance and the substance which gives the Pauly reaction from desiccated posterior lobes. The residue was extracted

repeatedly by water containing carbon dioxide. A ppt. was thrown down from this aqueous solution by $HgCl_2$. The colloidal solution produced by decomposition of the washed Hg precipitate hydrogen sulfide was evaporated to dryness and taken up with methyl alcohol, precipitated by ether and extracted by absolute ethyl alcohol. Further purification gave a white amorphous precipitate which possessed a marked pressor reaction and gave no Pauly reaction.

—F. A. H.

Administration of a pituitary extract and histamine in a case of diabetes insipidus. Gibson (R. B.) & Martin (F. T.), Arch. Int. Med. (Chicago), 1921, **27**, 351-360.

This paper reports the study of a severe case of diabetes insipidus with chronic syphilis in which the symptoms were not relieved by lumbar puncture, but when 1 cc. doses of pituitary extract (obstetrical) were administered subcutaneously temporary relief was obtained, in that the volume of the urine was reduced and the concentration increased. A normal 24-hour concentration and volume, however, was not obtained at any time. Histamine (one injection of 0.2 mg.) gave a similar but less effective result. When desiccated whole pituitary substance was given by mouth, a slight immediate effect was observed. As a result of the pituitary extract injections there was a lower nitrogen elimination with considerable retention, diminished ammonia and undetermined nitrogen, and a somewhat increased uric acid output; the nitrogen partition was nearly normal. Glycogenesis was not reduced. There was hypoglycemia. Blood urea, creatinine, plasma chlorides, and total plasma proteins were normal. There was a high blood uric acid.—F. S. H.

(SEX) Sexual differentiation in Rana Temporaria. I. The acting mechanism in over-ripe eggs (Experimentelle Untersuchungen über die sexuelle Differenzierumg bei Rana temporaria. I. Die Wirkungsmechanismus überreifer Eier). Adler (L.), Arch. f. d. ges. Physiol. (Berlin), 1920, **183**, 23-39.

An attempt to connect sex differentiation with thyroid structure. Thyroid change resembling that in Graves' disease is usually present in metamorphosed frogs from over-ripe eggs; most of such frogs are males.—A. T. C.

(SEX) Experimental Hermaphroditism (Experimenteller Hermaphroditismus). Sand (K.), Arch. f. d. ges. Physiol. (Berlin), 1918, **173**, 1-7.

Transplantation experiments on guinea-pigs and rats, if preceded by castration, lead successfully to hermaphroditic conditions S.'s results in general are in agreement with those of Steinach.

—A. T. C.

(SEX) Experimental Hermaphroditism (Bemerkung zur Arbeit von Knud Sand über experimentellen Hermaphroditism). Schultz (W.), Arch. f. d. ges. Physiol. (Berlin), 1920, **179**, 217-218.

A claim for priority over Steinach, especially as regards methods.—A. T. C.

Note on the SPERMATOGENESIS of the blind worm. (Study of the atypical seminal cells.) (Note sur la spermatogénese de l'orvet.) (Etude des cellules séminales atypiques.) Dalcq (A.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1302-1304.

Histological material only.—T. C. B.

(SPLEEN) Contribution to the study of anemias accompanying splenomegaly in the nursling (Contribution à l'ètude des anémies avec splénomégalie chez le nourriseon). Hallez (G. L.), Nourrisson (Paris), 1921, **9**, 24-39.

This paper gives a description of the pathological anatomy in cases of anemia accompanying splenomegaly in infants. In the **bone-marrow** the connective tissue is found to be thinned in certain places and apparently a hypergenesis of nucleated erythroblasts is present. The **thymus** is generally increased in volume, though the structure is normal.

The etiology seems largely to lie in the field of syphilitic disturbances. Treatment consists of anti-syphilitic medication when necessary and opotherapy with fresh bone-marrow substance. Splenectomy at this age is not indicated.—F. S. H.

Homeotransplantation and autotransplantation of the SPLEEN in rabbits. III. Further data on growth, permanence, effect of age and partial or complete removal of the spleen. Marine (D.), & Manley (O. T.), J. Exper. Med. (Balt.), 1920, **31**, 113-133.

The results of these experiments on rabbits show that the spleen homeografts do not differ from most other homeografts in that they do not persist beyond the usual 1 to 2 weeks common to such attempts, although the possible advantages of consanguinity, age and splenectomy were fully utilized. This is, however, in sharp contrast to **thyroid, sex gland** and **adrenal** cortex homeografts and suggests that spleen is stronger antigen and excites a greater degree of immunity more quickly. With autografts survival and growth are the rule, and failures are due to technical errors. Age is an important factor; the younger the rabbit the more growth is aided. This beneficial effect decreases gradually and becomes negligible after sexual maturity. Removal of the spleen is a powerful stimulus to the growth of transplants. The effect varies inversely with the age, and is unusually negligible after sexual maturity. This

suggests that the spleen is most important in early life and after sexual maturity is either unimportant or its functions may readily be assumed by other tissues. There is some indication that subcutaneous grafts react to infections in the same way as the intact spleen.—F. S. H.

(SYMPATHETIC GANGLIA) Are the superior cervical ganglia indispensable to the maintenance of life? Meltzer (I. J.), Proc. Nat. Acad. Sc. (Balt.), 1920, **6**, 532-539.

In studying certain phases of the "paradoxical" pupillary reaction at various times it was noticed that the animals died soon after the operation, if both superior cervical ganglia were removed, and that autopsy revealed the presence of pulmonary lesions—bronchopneumonia in the upper and middle lobes, and edema of the lower lobes. Experiments were, therefore, made to test the question which is the title of the paper. Of 28 rabbits in which the superior cervical ganglia were removed from both sides, 6 died in less than 24 hours, 9 died in less than 2 days, 5 in less than 3 days, 1 each in 4, 5, 6, 8 and 10 days. All had pulmonary lesions. Two cats died in less than 2 days. Experiments were made to eliminate the possible effects of injury to the vagus.

An hypothesis as to the mechanism by which the ganglia may control life is offered. Fibers from the ganglia reach the respiratory center, and the tonus of the central laryngeal control is maintained by continuous impulses from the superior cervical ganglia. After removal of the ganglia the laryngeal center loses its tonus and coordinating activity upon the laryngeal muscles during respiration. The loss of coordination gives rise to results similar to those following cutting of the vagi. The origin of the impulse is explained by comparing the ganglia to glands of internal secretion. In four rabbits the ganglia on both sides were torn away from their upper connections, but were left connected with the sympathetic nerve. Two ganglia from another rabbit were placed deeply in the wound before closing it. All four animals survived many weeks, and were killed by chloroform; the lungs were normal. These findings are considered suggestive.—T. C. B.

Some facts concerning the histology of the ectopic TESTICLE (Quelques faits concernant l'histologie du testicule ectopique). Michon (L.) & Porte (P.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1438-1439.

Histological material only.—T. C. B.

Note on simple hypertrophy of the THYMUS (Correlated from radiographic tables and clinical case descriptions) (Note sull' ipertrofia semplice del timo corredate da tavole radiografiche e de-

scrizione di casi clinici). Gatti (O.), Folia med. (Napoli), 1917, **3**, 436; 459; 473-479.

The author discusses the normal occurrence of the thymus in childhood and in the adult. This is followed by an extensive consideration of the results of compressions produced by hypertrophy of this gland, and concludes that the condition, as an etiological agent, is associated with the more common infectious inflamatory processes. After a brief historical survey of thymus compressions, the author takes up several related forms of respiratory disturbances, with special reference to a clinical case. A child, one month of age, made a peculiar rattling sound upon heavy breathing. The condition gradually became more and more severe, until it was permanent and continuous, giving rise to suffocation and cyanosis. The x-ray showed hypertrophy of the thymus. Treatment by radiotherapy resulted in complete recovery and the child when observed a year later was in perfect health with no signs of relapse.—D. P.

Status THYMOLYMPHATICUS. Hart (C.), Ztschr. f. ärztl. Fortbild. (Jena), 1920, **17**, 673-676; 697-700.

A general review without new data.—J. K.

Enlarged THYMUS gland in infancy and its treatment by radium. Brayton (H. W.) & Heublein (A. C.), Boston M. & S. J., 1919, **181**, 740-743.

A report of several cases where infantile thymic enlargement has been successfully treated with radium applications.—H. W.

The genesis of amphibian-neoteny. The physiology of the amphibian THYROID (Untersuchungen über die Entstehung der Amphibienneotenie. Zugleich, ein Beitrag zur Physiologie der Amphibienschilddrüse). Adler (L.), Arch. f. d. ges. Physiol (Bonn), 1916, **164**, 1-101.

Histological examination shows that the thyroids of frog larvae and metamorphosed frogs correspond to the climatic conditions of their surroundings. Frogs from the Alps have relatively large thyroids with many small vesicles, those from the Adriatic coast usually small thyroids with a few large vesicles, and those from middle Germany with an intermediate climate show an intermediate condition. With cultures kept at a temperature above optimum-growth is delayed, and metamorphosis still more delayed so that the metamorphosed frog is larger than normal; its thyroid is usually smaller, but of normal structure. With cultures kept at first at a low temperature (8° to 10°) and then changed to a high temperature (30° C.), metamorphosis is delayed and growth more so. The young frog is smaller than usual and in extreme cases dwarf frogs

are produced (which soon die). The thyroids show marked atrophy, in a large number of cases indicating a complete disorganization. In the reverse culture (hot-cold) metamorphosis is more greatly delayed, leading to larger animals. The thyroids are larger than normal; their structure resembles the initial stage of goiter. The colloid becomes more fluid. Since the thyroid shows such specific morphological changes under the influence of extreme temperature changes it is probable that slight temperature changes also produce a functional effect so that the amphibian thyroid can act as a regulatory mechanism.—A. T. C.

(THYROID) Contributions to the biochemistry of iodine. IV. The effect of thyroxin on growth in white rats and in rabbits. Cameron (A. T.) & Carmichael (J.), J. Biol. Chem. (Balt.), 1921, **46**, 35-56.

Using rat and rabbits as the experimental animals, the authors added to the diet of bread and milk certain amounts of thyroxin depending upon the daily body weight. Extensive tables are given of the growth of the animals as a whole and of the relative size of the various organs an autopsy of the treated subjects and the controls. The thyroxin-fed rats showed distinctly less fat than the control animals, but not so markedly as did rats that had received thyroid gland in the ratio of 1:5,000 of body weight. The thyroids of the treated rats were always paler in color than those of the controls. The results show conclusively that thyroxin produces a distinct decrease in growth-rate, and a hypertrophy of the liver, kidneys, heart, **spleen** and **adrenals.** The effect on the **testes** was uncertain, thus demonstrating that qualitatively thyroxin and thyroid produce the same results. It is evident, then, that thyroxin answers satisfactorily to all the tests to which it can be subjected, as to whether or not it is the essential chemical compound (autocoid, hormone) secreted by the thyroid gland.—F. S. H.

(THYROID) Delayed hereditary lues (Lues hereditaria tardia: Endocrinopatias. II. Tiroides). Castex (M. R.) & Waldorp (C. P.), Prensa med. Argent. (Buenos Aires), 1920, **7**, No. 5, July.

The stigmata of hereditary syphilis are in large part due to a thyroid dystrophy. The nasal hydrorrhea often has as its cause a hypo- or dysthyroidism. Mongolism is a dystrophy of endocrine origin produced by syphilis.—B. A. H.

(THYROID) Tuberculosis in a region of endemic goiter (La tuberculose dans une région à goitres endemiques). Coulaud, Bull. et mem. Soc. méd. d. hôp. d. Par., 1921, **45**, 5-8.

In the departments of the North, the Adrennes and l'Aisne goiters appeared more numerous after the German invasion than

formerly. Amenorrhea also was frequent which, due to the under nourishment of the individual, gave rise to a compensatory hyperthyroidism. One hundred families were examined and out of this number 220 individuals were goitrous, while some 230 persons in these families were tubercular. Coulaud summarizes by stating that both hypo- and hyperthyroid conditions were found in the goitrous families and that it is more a question of thyroidal families rather than goitrous families. Tuberculosis did not appear in the goitrous until the menopause, while the hypothyroid cases are, so to speak, never afflicted, if they are it is with latent types. The number of cases of tuberculosis observed were by and large in the non-goitrous or non-hypothyroid persons.—F. S. H.

Case of THYREOAPLASIA (Ein Fall von Thyreoaplasie). Falta, Wien. klin. Rundschau., 1919, **35**, 91.

See Endocrin., **4**, 166.

(THYROID) Graves' disease with unilateral exophthalmos (Ein Fall von Morbus Basedowii mit einseitigem Exophthalmus). Falta, Wien. klin. Rundschau, 1919, **33**, 90; Klin-therap. Wchnschr. (Berl.), 1919, **26**, 295.

See Endocrin., **4**, 165.

Concerning the diagnosis and treatment of HYPOTHYROIDISM. Janney (N. W.) & Henderson (H. E.), Arch. Int. Med. (Chicago), 1920, **26**, 297-318.

Studies are reported of 17 cases of latent and obvious hypothyroidism. The usual clinical history was written: physical examination, differential blood count, glucose tolerance test, and basal metabolism determinations were made. The authors consider that latent hypothyroidism is more frequent than generally supposed, since among 18 consecutive cases it was present in 12, four cases being dysthyroidism and only one presenting classical myxedematous symptoms. The analysis of the clinical data show that in over 50 per cent of the cases the following stigmata are present; history of obesity, particularly in early life; mental symptoms; marked liability to contract infections; hair anomalies; dry harsh skin with pigmentation and atrophy; cold extremities and cold skin generally; obesity; decreased size of thyroid; subnormal temperature, pulse and respiration. Of all the data, the lowered temperature, pulse and respiration occur most frequently. The basal metabolism rate is of great value in diagnosis and treatment, but cannot be considered as an absolute criterion. Usually the blood glucose tolerance test is abnormal in respect to the height of the curve and the delayed return to the normal level in cases of thyroid disease, but is only diagnostic of endocrine disease in general. There is no constant

relation demonstrable between the blood sugar curve and the metabolic rate in thyroid disease. Treatment of hypothyroidism is best carried out with thyroxin and controlled by basal metabolic rate determinations.—F. S. H.

The action of THYROID on tadpoles (Ueber die Wirkung der Schilddrüse auf Kaulquappen). Jarisch (A.), Arch. f. d. ges. Physiol. (Berlin), 1920, **179**, 159-176.

The larval organs of tadpoles disappear in shortest time when they are fed single large doses of thyroid. The retrogression affects the gills, with fatal results. By administration of oxygen the tadpoles can be kept alive. Retrogression and metamorphosis can be checked by different diets, the action of which is parallel to their protein-sparing properties. Corresponding food protects the tadpole from resorption of larval parts. Thyroid acts through its influence on metabolism. It increases catabolism and hence accelerates the resorption of larval organs. No direct action of thyroid on metamorphosis has been demonstrated.—A. T. C.

(THYROID) Symptoms of hyperthyroidism observed in exhausted soldiers. Johnson (W.), Arch. Diagn. (N. Y.), 1918-19, **11**, 260-268.

See Endocrin., **4**, 169.

(THYROID) Prophylaxis of Endemic Goiter (Zur prophylaxie des endemischen Kropfes). Klinger (R.), Corr. Bl. Schweiz. Aertz. (Basel), 1918, **48**, 546-548.

The plea is advanced for the use of sodium iodide as a prophylactic agent against endemic goiter. See later publication: abstracted in Endocrin., 1919, **3**, 585.—H. W.

(THYROID) The prevention of simple goiter (Die Prophylaxe des endemischen Kropfes). Klinger (R.), Schweiz. med. Wchnschr. (Basel), 1921, **51**, 12-15.

Klinger reports the results of the administration of small doses of iodine on the prevention of simple or endemic goiter in children in seven Swiss schools in the region around Zürich. His observations cover a period of 15 months. He used both sodium iodide and a proprietary organic preparation, "Iodostarin," preferring the latter because of the bitter taste of sodium iodide. He began the treatment with 30 mgm. (approx. ½ gr.) iodide at weekly intervals, and after three months reduced it to 10 mgm. weekly. Before beginning the prophylactic treatment he conducted a careful survey of the incidence of goiter among the children, classifying the condition of the thyroids in the following groups: (1) not or scarcely palpable;

(2) palpable but not enlarged; (3) slightly enlarged; (4) moderately enlarged; (5) large goiters. In some school districts as high as 95% of the children between the ages of 6-10 years had enlarged thyroids and in other districts as low as 82% at the time of the initial survey. The age group 10-14 years, as would be expected, showed still higher incidences of goiter even 100%. These percentages indicate a highly goiterous district. With such a high natural incidence of goiter his observations were confined largely to the **curative** rather than to the **prophylactic** effects of iodine. The curative effects are striking: Thus of 760 children 90% were goiterous at the first examination. After 15 months' treatment with 10 to 30 mgm. iodine as "iodostarin" weekly, only 28.3% were goiterous out of a total of 643 children examined. As striking results were obtained with sodium iodide in another school where a total of 60 mgm. of iodine per pupil was administered in six months. Thus of 179 pupils, of whom 90% were goiterous at the beginning of the feeding, only 41% were goiterous after six months. The point the author wishes to drive is that exceedingly small amounts of iodine (comparatively) are needed to produce these remarkable thyroid changes.

As to the form of iodine used, cheapness and convenience of administration should rule. Tablets are most convenient. In over 1000 cases observed for sixteen months, no untoward effects were noted—not even a single case of iodism, although carefully looked for. Attention of physicians is called to the fact that fears of untoward effects (iodism or iodin—Basedow) even from the use of excessive physiological amounts of iodine (3-5 mgms. weekly) are without foundation.

He concludes that endemic goiter in children may be completely controlled at a nominal cost by the simple expedient of giving 3 to 5 mgm. iodine once or twice weekly over a period of a month and repeated each Spring and Autumn. The carrying out of the prophylaxis should be placed in the hands of physicians, preferably the school and district physicians. With the state-wide use of prophylaxis, goiter could be eliminated, the general health standards improved and those mental and physical defects (cretinism, mutism, idiocy) so intimately associated with a deficiency of the internal secretion of the thyroid could be greatly reduced.—D. M.

(THYROID) Myxedema. Klinkert (H.), Ned. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 467.

A report of a patient with deafness and noises in the ears. The lips were thick, she lost her hair, showed a swollen tongue and a dry skin. After thyroid treatment, the myxedema, the deafness and the noises in the ears disappeared, but a tremor appeared, which may perhaps be considered as a symptom of Graves' disease.—J. K.

(THYROID) One thousand one hundred and forty-six goiters in one thousand seven hundred eighty-three persons. Levin (S.), Arch. Int. Med. (Chicago), 1921, **27**, 421-433.

"Obscurity and darkness in the field of medicine excite the profession to research." With this introductory remark Levin proceeds to tabulate and discuss the goiter incidence observed by him in the Great Lakes region. No selection was made of the subjects coming under examination. He divides his individuals into 3 groups. The first consists of those having simple goiter, giving no symptoms save an homogeneous enlargement of both lobes and isthmus that may be small, moderate or large. In this group he could place 682 cases or 38.2 per cent, of which 29.1 per cent were males and 45.5 per cent females. Group 2 consisted of cases where adenoma was present, whether small, large or moderate in size. Cystomas were included. In this class 420 goiters were found or 23.5 per cent of the total incidence, of which 15.0 per cent were males and 30.3 females. In group 3 were placed all those cases designated as colloid goiter. The state was determined by the firmer, doughy consistency of the gland. In the group 44 individuals were placed. That is to say, the class represented 2.5 per cent of the examined individuals. Of these 0.76 per cent were males and 3.8 per cent females. Levin concludes by stating that in a zone in which thyroid enlargements occur, as in the one he studied, there is a normal physiological hypertrophy of the gland and that this should not be called goiter, though it must be remembered that long continued enlargement means permanent enlargement. The incidence curves show that goiters increase in both sexes during puberty, and drop to a small degree after the growth of the individual is attained. The curve remains in the female for the child-bearing period, going down at about 38-40 years, when it rises again for the menopause. In the male the curve gradually drops till 35 or 40 years, when there is a small rise due to growths in the glands. The simple goiters maintain the high percentage till 35 years is attained and the adenoma and cystoma sustain the height of incidence curve after that age. The various water supplies—spring water or Lake Superior water—influence the enlargements of the thyroids the same.

—F. S. H.

Studies on compensatory hypertrophy of the THYROID gland. V. The effect of the administration of thyroid, THYMUS gland and tethelin and of a meat diet on the hypertrophy of the thyroid gland in guinea-pigs. Loeb (L.), J. Med. Research (Boston), 1920, **42**, 77-89.

L. found that the feeding of desiccated thyroid to guinea-pigs following extirpation of most of their thyroid glands markedly inhibited compensatory hypertrophy of the remaining fragment—an

additional confirmation of a long known fact. He fed large amounts of thyroid (8-12 grains over a period of 10-15 days) and examined the thyroid remnants after intervals of 17-29 days. Most of the animals lost weight. Thymus gland had no effect. Previous work by the author had suggested that potassium iodide might counteract the effect of thyroid feeding, but no experimental proof of this was obtained. The author thought he observed less compensatory hypertrophy in the warmer months (May to October) than in winter, thus tending to confirm in guinea-pigs the well established fact of seasonal variations in thyroid activity.

Tethelin, administered in 50 to 60 mgm. doses subcutaneously every three or four days to four guinea-pigs was without effect on the thyroid hypertrophy. Studies on the effect of a diet consisting principally of meat given during a period of three and one-half weeks was without effect on the compensatory hypertrophy of the thyroid gland.—D. M.

Heterotransplantation of the THYROID gland. Loeb (L.), J. Exper. Med. (Balt.), 1920, **31**, 765-784.

This paper deals with the heterotransplantation of the thyroid gland free from bacterial contamination in mammals. Thyroids were removed from guinea-pigs and transplanted into rats. In this series it was found that as late as 9 days after the transplantation a number of acini are preserved and mitoses occur. This is the latest term at which mitoses and living tissue are found. The conclusion is made that there is a general incompatability between the body fluids and the transplant. The destructive action of lymphocytes and connective tissue play only a minor part. In the second series thyroid glands from rabbits were transplanted into rats. Here living acini were found as late as 11 days, though mitoses were not observed after the ninth day, even at that time their presence was exceptional. Capillaries may grow actively in the tissue surrounding the transplant, but usually do not invade the implanted tissue. The third series consists of studies of the effects of the transplantation of thyroids from rabbits into guinea-pigs. The results were not as satisfactory as the previous attempts. Otherwise, the conditions are similar to those generally seen in heterotransplants. In a fourth series thyroids were removed from cats and then transplanted into rats. Here the results appear to be indicative of a better resistance of the transplants towards the destructive agencies of the host. Apparently the primary factor in the destruction of the heterotransplants is the injurious effects of the heterotoxins; these change the metabolism of the transplanted cells which now exert an effect upon the blood-vessels, connective tissue cells, and lymphocytes.—F. S. H.

(THYROID) Some points on the surgical treatment of goiter. Mackenty (J. E.), Laryngoscope (St. Louis), 1918, **27**, 912-914.

A discussion of operative procedures in the treatment of goiter in which is urged the work of goiter surgery be taken up by laryngologists.—H. W.

(THYROID) The nature of chemical heat-regulation. II. Physiological heat regulation (Ueber das Wesen der chemischen Wärmeregulation. II. Die physiologische Wärmeregulation). Mansfeld (G.) & v. Pap (L.), Arch f. d. ges. Physiol. (Berlin), 1920, **184**, 281-293.

Isolated hearts from cooled animals (rabbits) use 2 to 3 times as much sugar as those from animals kept at a summer temperature, while those from animals kept for some hours at 34° to 35° C. use scarcely any. The blood-serum of cooled animals raises the sugar-consumption of isolated hearts from warmed animals, and vice versa. Cooling of **thyroidectomized** animals does not increase the sugar-consumption of the exsected heart, and the serum of warmed thyroidectomized animals does not lower the sugar-consumption of isolated hearts from cooled normal animals. It is hence concluded that chemical regulation against heat and cold is brought about by two chemical substances, which control oxygen consumption of the organs; both hormones are probably thyroid products.—A. T. C.

The physiology of the THYROID. IX. A defense (Beiträge zur Physiologie der Schilddrüse. IX. Zur Abwehr). Mansfeld (G.), Arch. f. d. ges. Physiol. (Berlin), 1920, **181**, 249-270.

Controversial, defending previous conclusions against Hári (the same journal, vol. 176).—A. T. C.

(THYROID) Prevention of simple goiter in man. IV. Marine (D.) & Kimball (O. P.), Arch. Int. Med. (Chicago), 1920, **25**, 661-672.

Observations on the prevention of goiter in man on a large scale have extended over a period of thirty months. The results show that it may be prevented very simply and cheaply in normal individuals. While thyroid enlargements of adolescence are more common, they are not more important than those occurring in mother and fetus. Prevention of adolescent goiter is properly a public health problem, while the prevention of fetal and maternal thyroid enlargements is largely a responsibility of individual physicians. The presence of pathologic conditions may modify the result of the prophylactic treatment in individual cases. While such instances are rare, they are important and merit detailed reports. The treatment consists in the administration of iodine, by mouth, by inhalation, or by external application. The former is preferred for reasons of con-

venience, economy and dose regulation. An ounce of syrup of ferrous iodide or hydriodic acid given over a period of from 2 to 3 weeks repeated twice yearly is apparently ample. As a public health measure 2 grams of sodium iodide spread over a period of 2 weeks and repeated twice yearly has been successful. This dosage prevented enlargement of the thyroid in more than 99 per cent of the children in the mildly goitrous district studied.—F. S. H.

(THYROID) Exophthalmic goiter. Nye (H. W.), Med. Herald (Kansas City), 1920, **39**, 299-300.

A report of a case of exophthalmic goiter in a woman 32 years old with a pulse of 140 to 160, extreme nervousness, exophthalmus, severe headaches, glucosuria, etc. Removal of the thyroid was considered unadvisable because of the severe degree of toxicity. The superior thyroid arteries were ligated and the gland was injected with boiling water without beneficial results. Finally it was decided to try the effects of high frequency currents applied to the neck and also precussion of the seventh cervical vertebra, the rationale being "that the disease is an angio-paralytic affection and that stimulation of the vasomoter center in the cord by concussion of spinal processes of seventh cervical is beneficial." In addition the patient was given capsules of pancreatin. These treatments were continued for three months with the result that the menses returned, the pulse dropped to 80 or 90 and the patient declared herself well.

—C. W.

(THYROID) Substernal goiter, with pressure symptoms. Rachford (B.), Am. J. M. Sc. (Phila.), 1920, **160**, 410-414.

A clinical case of hyperthyroidism complicated by pressure paralysis of the right side of the diaphragm and right vocal cord and by displacement of the heart, showed fairly satisfactory recovery following treatment consisting of Roentgen ray, rest and medication.

—W. J. A.

Further experiments on the influence of fat- and lipoid-substances and of protein-free extracts of THYROID on metamorphosis and growth (Weitere Versuche über den Einfluss von Fett- und Lipoidsubstanzen sowie von enteiweissten Extrakten der Schilddrüse auf Entwicklung und Wachstum). Romeis (B.), Arch. f. d. ges. Physiol. (Berlin), 1918-19, **173**, 422-497.

Experiments with horse-thyroid extracts on **R. temporaria** tadpoles are reported in this paper. Various fractionations were made with acetone, alcohol, and ether, and the effects of the fractions on growth and metamorphosis are detailed. The fraction soluble in boiling alcohol and separating on cooling consists chiefly of fats and fatty acids and markedly inhibits both growth and metamorphosis.

After removal of substances soluble in ether, acetone, and absolute alcohol, alcohol-water extracts hasten metamorphosis and inhibit growth, producing the same effect as a 96 per cent alcoholic extract of fresh gland. Aqueous thyroid extract from which proteins have been completely precipitated strongly inhibits growth and metamorphosis. Thyreoglandol only accelerates metamorphosis when given in large doses over a long period, and then only slightly; growth is increased. The more completely protein is removed from aqueous thyroid extract the weaker is the metamorphosis acceleration; sometimes growth is increased. Since the action of solutions similarly treated, but in which proteins have been previously hydrolysed, markedly inhibits growth and promotes metamorphosis, it is suggested that similar hydrolytic cleavages take place in the production of the thyroid secretion.—A. T. C.

Syphilis of the THYROID (Syphilis van de Schildklier). Roorda Smit (J. H.), Ned. Tijdschr. v. Geneesk, (Haarlem), 1921, **65**, 156-159.

The author observed two cases of Graves' disease of syphilitic origin which were cured by anti-syphilitical treatment. Both patients had a psychosis which also disappeared after treatment.—J. K.

(THYROID) Improvement in Graves' disease subsequent to severe focal infection. Squier (T.), Am. J. M. Sc. (Phila.), 1920, **160**, 358-366.

Two cases of hyperthyroidism are cited in which complicating infections first caused a marked increase in the severity of the thyroid symptoms. This was followed, after the acute infection had subsided, by a striking improvement if not a cure. The author believes it is not improbable that the improvement seen is due to actual loss of secretory tissue through post-infectious sclerosis of the gland. —W. J. A.